

SUBSYS- fentanyl spray

Insys Therapeutics, Inc.

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use SUBSYS safely and effectively. See full prescribing information for SUBSYS.

SUBSYS® (fentanyl sublingual spray), CII

Initial U.S. Approval: 1968

WARNING: RISK OF RESPIRATORY DEPRESSION, MEDICATION ERRORS, ABUSE POTENTIAL

See full prescribing information for complete boxed warning.

- Due to the risk of fatal respiratory depression, SUBSYS is contraindicated in opioid non-tolerant patients (1) and in management of acute or postoperative pain, including headache/migraines. (4)
- Keep out of reach of children. (5.3)
- Use with CYP3A4 inhibitors may cause fatal respiratory depression. (7)
- When prescribing, do not convert patients on a mcg per mcg basis from any other oral transmucosal fentanyl product to SUBSYS. (5.1)
- When dispensing, do not substitute with any other fentanyl products. (5.1)
- Contains fentanyl, a Schedule II controlled substance with abuse liability similar to other opioid analgesics. (9.1)
- SUBSYS is available only through a restricted program called the TIRF REMS Access program. Outpatients, healthcare professionals who prescribe to outpatients, pharmacies, and distributors are required to enroll in the program. (5.10)

INDICATIONS AND USAGE

SUBSYS is an opioid agonist indicated for the management of breakthrough pain in cancer patients 18 years of age and older who are already receiving and who are tolerant to opioid therapy for their underlying persistent cancer pain. Patients must remain on around-the-clock opioids when taking SUBSYS. (1)

Limitations of Use:

SUBSYS may be dispensed only to patients enrolled in the TIRF REMS ACCESS program.

DOSAGE AND ADMINISTRATION

- Patients must require and use around-the-clock opioids when taking SUBSYS. (1)
- Initial dose of SUBSYS: 100 mcg.
- Individually titrate to a tolerable dose that provides adequate analgesia using a single SUBSYS dose per breakthrough cancer pain episode. (2)
- No more than two doses can be taken per breakthrough pain episode. (2.2)
- Wait at least 4 hours before treating another episode of breakthrough pain with SUBSYS. (2.3)
- Limit consumption to four or fewer doses per day once successful dose is found. (2.3)

DOSAGE FORMS AND STRENGTHS

- Sublingual spray in 100 mcg, 200 mcg, 400 mcg, 600 mcg, 800 mcg dosage strengths. (3)

CONTRAINDICATIONS

- Opioid non-tolerant patients. (4)
- Management of acute or postoperative pain including headache/migraine and dental pain (4)
- Intolerance or hypersensitivity to fentanyl, SUBSYS, or its components. (4)

WARNINGS AND PRECAUTIONS

- Clinically significant respiratory and CNS depression can occur. Monitor patients accordingly. (5.1)
- Full and consumed SUBSYS units contain medicine that can be fatal to a child. Ensure proper storage and disposal. (5.3, 16.2)
- Use with other CNS depressants and moderate or strong CYP450 3A4 inhibitors may increase depressant effects including respiratory depression, hypotension, and profound sedation. Consider dosage adjustments if warranted. (5.4)
- Titrate SUBSYS cautiously in patients with chronic obstructive pulmonary disease or preexisting medical conditions predisposing them to respiratory depression and in patients susceptible to intracranial effects of CO₂ retention. (5.6, 5.7)

----- ADVERSE REACTIONS -----

Most common adverse reactions during treatment (frequency $\geq 5\%$): vomiting, nausea, constipation, dyspnea, and somnolence. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Insys Therapeutics, Inc., at 1-855-978-2797 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----- DRUG INTERACTIONS -----

- Boxed Warning and Warnings and Precautions (5.4, 7)

----- USE IN SPECIFIC POPULATIONS -----

- Safety and effectiveness in pediatric patients below 18 years of age have not been established. (8.4)
- Administer SUBSYS with caution to patients with liver or kidney dysfunction. (8.6)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

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FULL PRESCRIBING INFORMATION

WARNING: RISK OF RESPIRATORY DEPRESSION, MEDICATION ERRORS, ABUSE POTENTIAL

Respiratory Depression

Fatal respiratory depression has occurred in patients treated with transmucosal immediate-release fentanyl products such as SUBSYS, including following use in opioid non-tolerant patients and improper dosing. The substitution of SUBSYS for any other fentanyl product may result in fatal overdose.

Due to the risk of respiratory depression, SUBSYS is contraindicated in the management of acute or postoperative pain including headache/migraine and in opioid non-tolerant patients.

Death has been reported in children who have accidentally ingested transmucosal immediate-release fentanyl products. SUBSYS must be kept out of reach of children. *[see Patient Counseling Information (17) and How Supplied/Storage and Handling (16.1)]*

The concomitant use of SUBSYS with CYP3A4 inhibitors may result in an increase in fentanyl plasma concentrations, and may cause potentially fatal respiratory depression *[see Drug Interactions (7)]*.

Medication Errors

Substantial differences exist in the pharmacokinetic profile of SUBSYS compared to other fentanyl products that result in clinically important differences in the extent of absorption of fentanyl that could result in fatal overdose.

- When prescribing, do not convert patients on a mcg per mcg basis from any other fentanyl products to SUBSYS. *[see Dosage and Administration (2.1), Warnings and Precautions (5.2,) and Clinical Pharmacology (12.3)]*
- When dispensing, do not substitute a SUBSYS prescription for other fentanyl products.

Abuse Potential

SUBSYS contains fentanyl, an opioid agonist and a Schedule II controlled substance, with an abuse liability similar to other opioid analgesics.

SUBSYS can be abused in a manner similar to other opioid agonists, legal or illicit. This should be considered when prescribing or dispensing SUBSYS in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse or diversion.

Because of the risk for misuse, abuse, addiction, and overdose, SUBSYS is available only through a restricted program required by the Food and Drug Administration, called a Risk Evaluation and Mitigation Strategy (REMS). Under the Transmucosal Immediate-Release Fentanyl (TIRF) REMS Access program, outpatients, healthcare professionals who prescribe to outpatients, pharmacies, and distributors must enroll in the program. *[See Warnings and Precautions (5.10)]* Further information is available at www.TIRFREMSaccess.com or by calling 1-866-822-1483.

1 INDICATIONS AND USAGE

SUBSYS is indicated for the management of breakthrough pain in adult cancer patients who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain. Patients considered opioid tolerant are those who are taking around-the-clock medicine consisting of at least 60 mg of oral morphine daily, at least 25 mcg of transdermal fentanyl/hour, at least 30 mg of

oral oxycodone daily, at least 8 mg of oral hydromorphone daily or an equianalgesic dose of another opioid daily for a week or longer. Patients must remain on around-the-clock opioids when taking SUBSYS.

This product **must not** be used in opioid non-tolerant patients because life-threatening respiratory depression and death could occur at any dose in patients not on a chronic regimen of opioids. For this reason, SUBSYS is contraindicated in the management of acute or postoperative pain.

SUBSYS is intended to be used only in the care of cancer patients and only by oncologists and pain specialists who are knowledgeable of and skilled in the use of Schedule II opioids to treat cancer pain.

Limitations of Use:

As part of the Transmucosal Immediate-Release Fentanyl (TIRF) REMS ACCESS Program, SUBSYS may be dispensed only to outpatients enrolled in the program. *[see Warnings and Precautions (5.10)]*. For inpatient administration (e.g. hospitals, hospices, and long-term care facilities that prescribe for inpatient use) of SUBSYS, patient enrollment is not required.

2 DOSAGE AND ADMINISTRATION

Healthcare professionals who prescribe SUBSYS on an outpatient basis must enroll in the TIRF REMS ACCESS program and comply with the requirements of the REMS to ensure safe use of SUBSYS. *[see Warnings and Precautions (5.10)]*

As with all opioids, the safety of patients using such products is dependent on health care professionals prescribing them in strict conformity with their approved labeling with respect to patient selection, dosing, and proper conditions for use.

2.1 Initial Dose

SUBSYS is not bioequivalent with other fentanyl products. Do not convert patients on a mcg per mcg basis from other fentanyl products. There are no conversion directions available for patients on any other fentanyl products other than Actiq. (Note: This includes oral, transdermal, or parenteral formulations of fentanyl.)

Patients on Actiq

The initial dose of SUBSYS is always 100 mcg with the only exception of patients already using Actiq.

- a. For patients being converted from Actiq, prescribers must use the Initial Dosing Recommendations for Patients on Actiq table below (Table 1). Patients must be instructed to stop the use of Actiq and dispose of any remaining units.

Table 1. Initial Dosing Recommendations for Patients on ACTIQ

Current ACTIQ Dose (mcg)	Initial SUBSYS Dose (mcg)
200	100 mcg spray
400	100 mcg spray
600	200 mcg spray
800	200 mcg spray
1200	400 mcg spray
1600	400 mcg spray

- b. For patients converting from **Actiq doses 400 mcg and below**, titration should be initiated with 100 mcg SUBSYS and should proceed using multiples of this strength.

- c. For patients converting from **Actiq doses of 600 and 800 mcg**, titration should be initiated with 200 mcg SUBSYS and should proceed using multiples of this strength.
- d. For patients converting from **Actiq doses of 1200 and 1600 mcg**, titration should be initiated with 400 mcg SUBSYS and should proceed using multiples of this strength.

All Other Patients

Individually titrate SUBSYS to a dose that provides adequate analgesia and minimizes side effects. The initial dose of SUBSYS to treat episodes of breakthrough cancer pain is **always** 100 mcg. **When prescribing, do not switch patients on a mcg per mcg basis from any other oral transmucosal fentanyl product to SUBSYS** as SUBSYS is not equivalent on a mcg per mcg basis with any other fentanyl product [see *Warnings and Precautions (5.2) and Clinical Pharmacology (12.3)*].

Prescribe an initial titration supply of 100 mcg SUBSYS units, which limits the number of units in the home during titration.

Avoid prescribing a higher dose until patients have used up all units to prevent confusion and possible overdose.

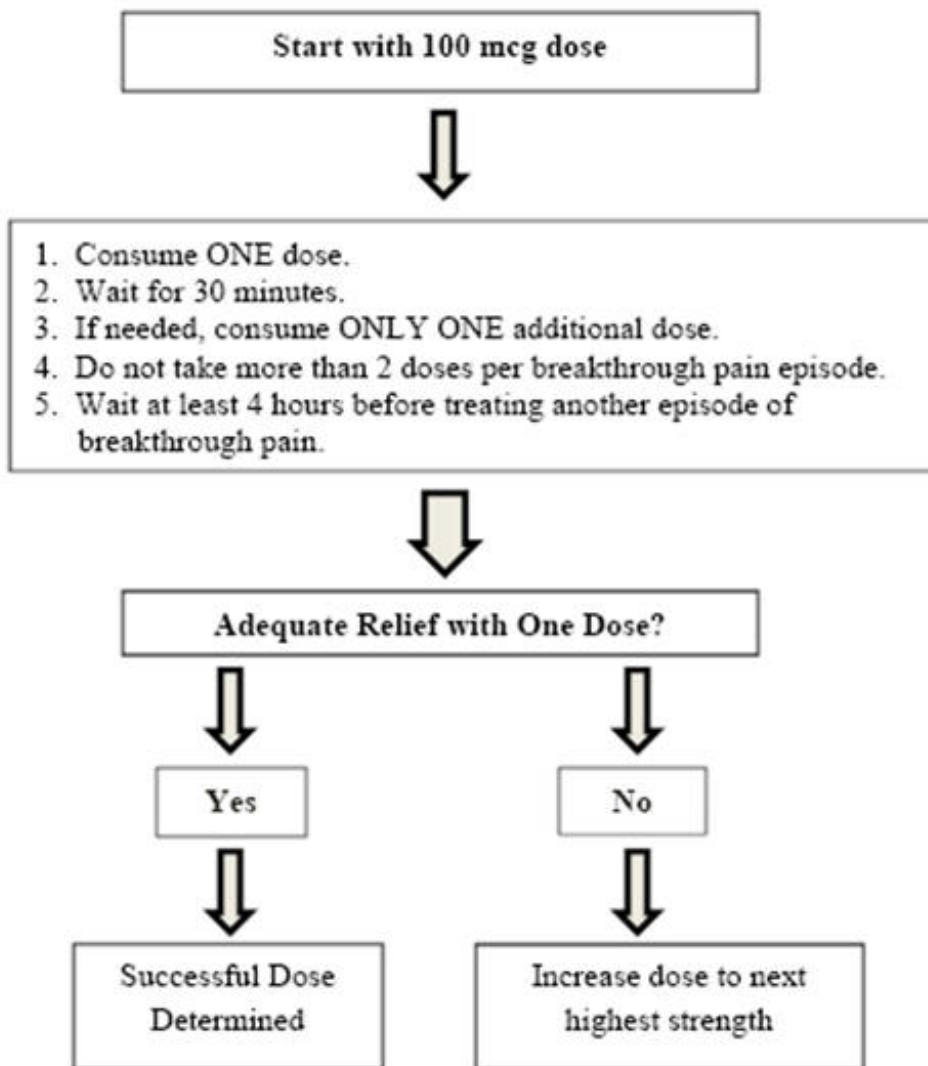
2.2 Dose Titration

- a. From the 100 mcg initial dose, closely follow patients and change the dosage level until the patient reaches a dose that provides adequate analgesia using a single SUBSYS dose per breakthrough cancer pain episode with tolerable side effects. Patients should record their use of SUBSYS over several episodes of breakthrough cancer pain and review their experience with their physicians to determine if a dosage adjustment is warranted.
- b. For each breakthrough pain episode treated, if pain is not relieved after 30 minutes, patients may take **ONLY ONE** additional dose of the same strength for that episode. Thus patients should take a maximum of two doses of SUBSYS for any breakthrough pain episode.
- c. Patients **MUST** wait **at least 4 hours** before treating another episode of breakthrough pain with SUBSYS.
- d. If there is a need to titrate to a 200 mcg dose, prescribe 200 mcg SUBSYS units.
- e. Subsequent titration steps are 400 mcg, 600 mcg, 800 mcg, 1200 mcg and 1600 mcg. See Table 2.
- f. To reduce the risk of overdose during titration, patients should have only one strength of SUBSYS available at any time.

Table 2. Titration Steps

SUBSYS DOSE	Using
100 mcg	1 × 100 mcg unit
200 mcg	1 × 200 mcg unit
400 mcg	1 × 400 mcg unit
600 mcg	1 × 600 mcg unit
800 mcg	1 × 800 mcg unit
1200 mcg	2 × 600 mcg unit
1600 mcg	2 × 800 mcg unit

SUBSYS Titration Process



2.3 Maintenance Dosing

Once titrated to a dose that provides adequate pain relief and tolerable side effects, patients should generally use **ONLY ONE** SUBSYS dose of the appropriate strength per breakthrough pain episode.

On those occasions when the breakthrough pain episode is not relieved within 30 minutes after administration of the SUBSYS dose, the patient may take **ONLY ONE** additional dose using the same strength for that episode.

Patients **MUST** wait **at least 4 hours** before treating another episode of breakthrough pain with SUBSYS. Once a successful dose has been found, patients should limit consumption to four or fewer doses per day.

Dosage adjustment of SUBSYS may be required in some patients in order to continue to provide adequate relief of breakthrough pain.

If signs of excessive opioid effects appear following administration of a single SUBSYS dose, subsequent doses should be decreased.

Generally, only increase the SUBSYS dose when a single administration of the current dose fails to adequately treat the breakthrough pain episode for several consecutive episodes.

If the patient experiences greater than four breakthrough pain episodes per day, the dose of the maintenance (around-the-clock) opioid used for persistent pain should be re-evaluated. In addition, if pain worsens, re-evaluate the patient for changes in the underlying pain condition.

2.4 Administration of SUBSYS

The blister package should be opened with scissors immediately prior to product use. The patient should carefully spray the contents of the unit into his or her mouth underneath the tongue.

2.5 Disposal of SUBSYS

Patients and caregivers must be advised to dispose of used unit dose systems immediately after use and any unneeded unit dose systems remaining from a prescription as soon as they are no longer needed. Consumed units represent a special risk because they are no longer protected by the child resistant blister package, yet may contain enough medicine to be fatal to a child. *[see Patient Counseling Information (17)].*

Charcoal-lined disposal pouches are provided with every carton dispensed. A charcoal-lined disposal pouch is to be used by patients or their caregivers to dispose of the contents of any unneeded unit dose systems when they are no longer needed. Instructions for usage of the charcoal-lined disposal pouch are included in the *Medication Guide and Instructions for Use*.

2.6 Oral Mucositis

In cancer patients with mucositis, exposure to SUBSYS was greater than in patients without mucositis. For patients with Grade 1 mucositis, the increased maximum serum concentration and overall exposure requires closer monitoring for respiratory depression and central nervous system depression, particularly during initiation of therapy with SUBSYS. For patients with Grade 2 mucositis or higher, avoid use of SUBSYS unless the benefits outweigh the potential risk of respiratory depression from increased exposure. *[see Clinical Pharmacology (12.3)]*

3 DOSAGE FORMS AND STRENGTHS

SUBSYS is a sublingual spray available in 100 mcg, 200 mcg, 400 mcg, 600 mcg, 800 mcg strengths *[see How Supplied (16.3) and Storage and Handling (16.1)]*.

4 CONTRAINDICATIONS

SUBSYS is contraindicated:

- in opioid non-tolerant patients.
- in the management of acute or postoperative pain including headache/migraine. Life-threatening respiratory depression and death could occur at any dose in opioid non-tolerant patients.
- in patients with known intolerance or hypersensitivity to any of its components or the drug fentanyl. Anaphylaxis and hypersensitivity have been reported in association with the use of other oral transmucosal fentanyl products.

5 WARNINGS AND PRECAUTIONS

See Boxed Warning - WARNING RISK OF RESPIRATORY DEPRESSION, MEDICATION ERRORS, ABUSE POTENTIAL

5.1 Respiratory Depression

Respiratory depression is the chief hazard of opioid agonists, including fentanyl, the active ingredient in SUBSYS. Respiratory depression is more likely to occur in patients with underlying respiratory disorders and elderly or debilitated patients, usually following large initial doses in opioid non-tolerant patients, or when opioids are given in conjunction with other drugs that depress respiration.

Respiratory depression from opioids is manifested by a reduced urge to breathe and a decreased rate of respiration, often associated with the "sighing" pattern of breathing (deep breaths separated by

abnormally long pauses). Carbon dioxide retention from opioid-induced respiratory depression can exacerbate the sedating effects of opioids. This makes overdoses involving drugs with sedative properties and opioids especially dangerous.

5.2 Important Information Regarding Prescribing and Dispensing

SUBSYS is not bioequivalent with other fentanyl products. Do not convert patients on a mcg per mcg basis from other fentanyl products.

When dispensing, DO NOT substitute a SUBSYS prescription for any other fentanyl product. Substantial differences exist in the pharmacokinetic profile of SUBSYS compared to other fentanyl products that result in clinically important differences in the rate and extent of absorption of fentanyl. **As a result of these differences, the substitution of the same dose of SUBSYS for the same dose of any other fentanyl product may result in a fatal overdose.**

There are no conversion directions available for patients on any other fentanyl products. (Note: This includes oral, transdermal, or parenteral formulations of fentanyl.) All patients should be titrated from the 100 mcg dose. Titrate each patient individually to provide adequate analgesia while minimizing side effects. *[See Dosage and Administration (2.1) and Clinical Pharmacology (12.3)]*

5.3 Patient/Caregiver Instructions

Patients and their caregivers must be instructed that SUBSYS contains a medicine in an amount which can be fatal to a child. Death has been reported in children who have accidentally ingested transmucosal immediate-release fentanyl products. Patients and their caregivers must be instructed to keep both used and unused dosage units out of the reach of children. All used units should be disposed of immediately after use as they represent a special risk to children. *[see How Supplied/Storage and Handling (16.1, 16.2), Patient Counseling Information (17), and Medication Guide].*

Physicians and dispensing pharmacists must specifically question patients or caregivers about the presence of children in the home (on a full time or visiting basis) and counsel them regarding the dangers to children from inadvertent exposure.

SUBSYS could be fatal to individuals for whom it is not prescribed and for those who are not opioid-tolerant.

5.4 Additive CNS Depressant Effects

The concomitant use of SUBSYS with other CNS depressants, including other opioids, sedatives or hypnotics, general anesthetics, phenothiazines, tranquilizers, skeletal muscle relaxants, sedating antihistamines, and alcoholic beverages may produce increased depressant effects (e.g., respiratory depression, hypotension, and profound sedation). Concomitant use with strong and moderate inhibitors of CYP450 3A4 isoform (e.g., erythromycin, ketoconazole, and certain protease inhibitors) may increase fentanyl levels, resulting in increased depressant effects *[see Drug Interactions (7)]*.

Patients on concomitant CNS depressants must be monitored for a change in opioid effects. Consideration should be given to adjusting the dose of SUBSYS if warranted.

5.5 Effects on Ability to Drive and Use Machines

Opioid analgesics impair the mental and/or physical ability required for the performance of potentially dangerous tasks (e.g., driving a car or operating machinery). Warn patients taking SUBSYS of these dangers and counsel them accordingly.

5.6 Chronic Pulmonary Disease

Because potent opioids can cause respiratory depression, titrate SUBSYS with caution in patients with chronic obstructive pulmonary disease or preexisting medical conditions predisposing them to respiratory depression. In such patients, even normal therapeutic doses of SUBSYS may further

decrease respiratory drive to the point of respiratory failure.

5.7 Head Injuries and Increased Intracranial Pressure

Administer SUBSYS with extreme caution in patients who may be particularly susceptible to the intracranial effects of CO₂ retention such as those with evidence of increased intracranial pressure or impaired consciousness. Opioids may obscure the clinical course of a patient with a head injury and should be used only if clinically warranted.

5.8 Cardiac Disease

Intravenous fentanyl may produce bradycardia. Therefore, use SUBSYS with caution in patients with bradyarrhythmias.

5.9 MAO Inhibitors

SUBSYS is not recommended for use in patients who have received MAO inhibitors within 14 days, because severe and unpredictable potentiation by MAO inhibitors has been reported with opioid analgesics.

5.10 Transmucosal Immediate Release Fentanyl (TIRF) Risk Evaluation and Mitigation Strategy (REMS) ACCESS Program

Because of the risk of misuse, abuse, addiction and overdose [*see Drug Abuse and Dependence (9)*], SUBSYS is available only through a restricted program under a REMS called the TIRF REMS ACCESS program. Under the TIRF REMS ACCESS program, outpatients, prescribers who prescribe to outpatients, pharmacies, and distributors must enroll in the program. For inpatient administration (e.g. hospitals, hospices, and long-term care facilities that prescribe for inpatient use) of SUBSYS, patient and prescriber enrollment is not required.

Required components of the TIRF REMS ACCESS program are:

- Healthcare professionals who prescribe SUBSYS must review the prescriber educational materials for the TIRF REMS ACCESS program, enroll in the program, and agree to comply with the REMS requirements.
- To receive SUBSYS, patients must understand the risks and benefits and sign a Patient-Prescriber Agreement.
- Pharmacies that dispense SUBSYS must enroll in the program and agree to comply with the REMS requirements.
- Wholesalers and distributors that distribute SUBSYS must enroll in the program and distribute only to authorized pharmacies.

Further information, including a list of qualified pharmacies/distributors, is available at www.TIRFREMSaccess.com or by calling 1-866-822-1483.

6 ADVERSE REACTIONS

6.1 Clinical Studies Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety of SUBSYS has been evaluated in a total of 359 opioid-tolerant patients with breakthrough cancer pain. The duration of SUBSYS use varied during the open-label study. Safety data from a long-term extension study showed that the average duration of therapy in the open-label study was 66 days. The maximum duration of therapy was 149 days. The dose range studied in these trials ranged from 100 mcg per dose to 1600 mcg per dose.

The most commonly observed adverse reactions seen with SUBSYS are typical opioid side effects such as nausea, vomiting, somnolence, and constipation. Expect opioid side effects and manage them accordingly.

The most serious adverse reactions associated with all opioids including SUBSYS are respiratory depression (potentially leading to apnea or respiratory arrest), circulatory depression, hypotension, and shock. Follow all patients for symptoms of respiratory depression.

The most common adverse reaction leading to discontinuation of SUBSYS was nausea. There were also adverse reactions of abdominal distension, anorexia, confusional state, disorientation, somnolence, and constipation.

The clinical trials of SUBSYS were designed to evaluate safety and efficacy in treating breakthrough cancer pain; all patients were also taking concomitant opioids, such as sustained-release morphine or transdermal fentanyl, for their persistent cancer pain. The adverse event data presented here reflect the actual percentage of patients experiencing each adverse effect among patients who received SUBSYS for breakthrough cancer pain along with a concomitant opioid for persistent cancer pain.

Table 3 lists adverse reactions with an overall frequency of 5% or greater that occurred during titration in the clinical trials. Adverse reactions are listed in descending order of frequency within each system organ class.

Table 3. Percent of Patients with Specific Adverse Events During Titration in the Clinical Trials (Events in 5% or More of Patients)

System Organ Class	Titration n=359 (%)
Gastrointestinal Disorders	
Nausea	47 (13.1%)
Vomiting	37 (10.3%)
Constipation	18 (5.0%)
Nervous System Disorders	
Somnolence	34 (9.5%)
Dizziness	26 (7.2%)

A patient was counted only once within each category.

The following adverse reactions occurred during titration in the clinical trials with an overall frequency of 1% or greater and are listed in descending order of frequency within each system organ class.

Cardiac Disorders: Tachycardia

Gastrointestinal Disorders: Diarrhea, stomatitis, dry mouth

General Disorders and Administration Site Conditions: Application site irritation, pyrexia, edema peripheral, fatigue, asthenia

Metabolism and Nutrition Disorders: Decreased appetite

Nervous System Disorders: Lethargy, sedation, tremor, headache

Psychiatric Disorders: Depression, confusional state, hallucination, insomnia

Respiratory, Thoracic and Mediastinal Disorders: Dyspnea

Skin and Subcutaneous Tissue Disorders: Pruritus

The following reactions occurred during titration in the clinical trials with an overall frequency of less than 1% and are listed in descending order of frequency within each system organ class.

Eye Disorders: Vision blurred, dry eye

Gastrointestinal Disorders: Abdominal pain

Infections and Infestations: Oral candidiasis, cellulitis

Injury, Poisoning and Procedural Complications: Fall

Metabolism and Nutrition Disorders: Dehydration, anorexia

Musculoskeletal and Connective Tissue Disorders: Back pain, arthralgia, joint swelling

Psychiatric Disorders: Anxiety, agitation

Renal and Urinary Disorders: Urinary retention

Respiratory, Thoracic and Mediastinal Disorders: Cough, increased bronchial secretion, dysphonia, pharyngolaryngeal pain

Skin and Subcutaneous Tissue Disorders: Hyperhidrosis

Vascular Disorders: Hot flush

Table 4 lists adverse reactions with an overall frequency of 5% or greater for the total safety database subsequent to titration during the clinical trials.

Table 4. Adverse Reactions Subsequent to Titration in 5% or More of Patients

System Organ Class	Dosing n=269
Gastrointestinal Disorders	
Vomiting	43 (16.0%)
Nausea	28 (10.4%)
Constipation	28 (10.4%)
General Disorders and Administration Site Conditions	
Asthenia	26 (9.7%)
Respiratory, Thoracic and Mediastinal Disorders	
Dyspnea	28 (10.4%)
Psychiatric Disorders	
Anxiety	16 (5.9%)

A patient was counted only once within each category.

The following adverse reactions occurred during the dosing period of the clinical trial with an overall frequency of 1% or greater and are listed in descending order of frequency within each system organ class.

Blood and Lymphatic System Disorders: Anemia, neutropenia, lymphadenopathy, thrombocytopenia, leukopenia

Cardiac Disorders: Tachycardia, sinus tachycardia

Gastrointestinal Disorders: Diarrhea, stomatitis, abdominal pain, abdominal distension, gastritis, dysphagia, dyspepsia, gastroesophageal reflux disease, ascites, hematemesis

General Disorders and Administration Site Conditions: Edema peripheral, fatigue, pyrexia, chest pain, drug withdrawal syndrome, chills, irritability, malaise, application site irritation

Infections and Infestations: Oral candidiasis, pneumonia, urinary tract infection, oral herpes, gastroenteritis, laryngitis

Injury, Poisoning and Procedural Complications: Contusion

Investigations: Weight decreased, aspartate aminotransferase increased, blood alkaline phosphatase increased, blood glucose increased, blood lactate increased

Metabolism and Nutrition Disorders: Anorexia, dehydration, hypokalemia, decreased appetite, hyponatremia, hypocalcemia, hypoalbuminemia, cachexia

Musculoskeletal and Connective Tissue Disorders: Back pain, arthralgia, muscular weakness

Nervous System Disorders: Hypoesthesia, lethargy, sedation, tremor, somnolence, headache, dizziness

Psychiatric Disorders: Depression, restlessness, agitation, confusional state, insomnia, hallucination, disorientation

Renal and Urinary Disorders: hypertension, hypotension

Respiratory, Thoracic and Mediastinal Disorders: Cough, increased bronchial secretion, wheezing, pharyngolaryngeal pain, hypoxia, dyspnea exertional

Skin and Subcutaneous Tissue Disorders: hyperhidrosis, pruritus

In a single-dose mucositis study, a group of patients with Grade 1 or 2 oral mucositis (n=9) and without oral mucositis (n=9) were included in a clinical trial designed to support the safety of SUBSYS. Two of the nine subjects with mucositis (one with Grade 1 and one with Grade 2) reported a burning sensation in the oral mucosa after treatment. Both of these events were considered mild and probably related to treatment. There was no change in grade of mucositis after treatment for any subject.

7 DRUG INTERACTIONS

Fentanyl is metabolized mainly via the human cytochrome P450 3A4 isoenzyme system (CYP3A4); therefore potential interactions may occur when SUBSYS is given concurrently with agents that affect CYP3A4 activity.

The concomitant use of SUBSYS with strong CYP3A4 inhibitors (e.g., ritonavir, ketoconazole, itraconazole, troleandomycin, clarithromycin, nelfinavir, and nefazodone) or moderate CYP3A4 inhibitors (e.g., amprenavir, aprepitant, diltiazem, erythromycin, fluconazole, fosamprenavir, and verapamil) may result in increased fentanyl plasma concentrations, potentially causing serious adverse drug effects including fatal respiratory depression. Patients receiving SUBSYS concomitantly with moderate or strong CYP3A4 inhibitors should be carefully monitored for an extended period of time. Dosage increase should be done conservatively.

The concomitant use of SUBSYS with CYP3A4 inducers (e.g., barbiturates, carbamazepine, efavirenz, glucocorticoids, modafinil, nevirapine, oxcarbazepine, phenobarbital, phenytoin, pioglitazone, rifabutin, rifampin, St. John's wort, or troglitazone) may result in a decrease in fentanyl plasma concentrations, which could decrease the efficacy of SUBSYS. Patients receiving SUBSYS who stop therapy with, or decrease the dose of, CYP3A4 inducers should be monitored for signs of increased SUBSYS activity and the dose of SUBSYS should be adjusted accordingly.

Concomitant use of SUBSYS with an MAO inhibitor, or within 14 days of discontinuation, is not recommended [see *Warnings and Precautions* (5.9)].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

There are no adequate and well-controlled studies in pregnant women.

SUBSYS should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. No epidemiological studies of congenital anomalies in infants born to women treated with fentanyl during pregnancy have been reported.

Chronic maternal treatment with fentanyl during pregnancy has been associated with transient respiratory depression, behavioral changes, or seizures in newborn infants characteristic of neonatal abstinence syndrome.

In women treated acutely with intravenous or epidural fentanyl during labor, symptoms of neonatal respiratory or neurological depression were no more frequent than would be expected in infants of untreated mothers.

Transient neonatal muscular rigidity has been observed in infants whose mothers were treated with intravenous fentanyl.

Fentanyl is embryocidal in rats as evidenced by increased resorptions in pregnant rats at doses of 30 mcg/kg intravenously or 160 mcg/kg subcutaneously. Conversion to human equivalent doses indicates this is within the range of the human recommended dosing for SUBSYS.

Fentanyl citrate was not teratogenic when administered to pregnant animals. Published studies demonstrated that administration of fentanyl (10, 100, or 500 mcg/kg/day) to pregnant rats from day 7 to 21, of their 21 day gestation, via implanted microosmotic minipumps was not teratogenic (the high dose was approximately 3-times the human dose of 1600 mcg per pain episode on a mg/m² basis). Intravenous administration of fentanyl (10 or 30 mcg/kg) to pregnant female rats from gestation day 6 to 18, was embryo or fetal toxic, and caused a slightly increased mean delivery time in the 30 mcg/kg/day group, but was not teratogenic.

8.2 Labor and Delivery

Fentanyl readily passes across the placenta to the fetus; therefore do not use SUBSYS during labor and delivery since it may cause respiratory depression in the fetus or in the newborn infant.

8.3 Nursing Mothers

Fentanyl is excreted in human milk; therefore, do not use SUBSYS in nursing women because of the possibility of sedation and/or respiratory depression in their infants. Symptoms of opioid withdrawal may occur in infants at the cessation of nursing by women using SUBSYS.

8.4 Pediatric Use

Safety and efficacy in pediatric patients below the age of 18 years have not been established.

8.5 Geriatric Use

Of the 359 patients in clinical studies of SUBSYS in breakthrough cancer pain, 27% were 60 years of age and older, 17% were 65 years of age and older, and 3% were 75 years of age and older. No difference was noted in the safety profile of the group over 65 years of age as compared to younger patients in SUBSYS clinical trials.

Elderly patients have been shown to be more sensitive to the effects of fentanyl when administered intravenously, compared with the younger population. Therefore, monitor patients for respiratory depression and CNS effects when titrating SUBSYS in elderly patients.

8.6 Patients with Renal or Hepatic Impairment

Insufficient information exists to make recommendations regarding the use of SUBSYS in patients with impaired renal or hepatic function. Fentanyl is metabolized primarily via the human CYP450 3A4

isoenzyme system and mostly eliminated in urine. If the drug is used in these patients, monitor patients closely for signs of respiratory and central nervous system depression.

8.7 Gender

Both male and female opioid tolerant patients with cancer were studied for the treatment of breakthrough cancer pain. No clinically relevant gender differences were noted either in dosage requirement or in observed adverse reactions.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

Fentanyl is a Schedule II controlled substance that can produce drug dependence of the morphine type. SUBSYS may be subject to misuse, abuse and addiction.

9.2 Abuse and Addiction

Concerns about abuse, addiction, and diversion should not prevent the proper management of pain. However, all patients treated with opioids require careful monitoring for signs of abuse and addiction, because use of opioid analgesic products carries the risk of addiction even under appropriate medical use.

Addiction is a primary, chronic, neurobiologic disease, with genetic, psychosocial, and environmental factors influencing its development and manifestations. It is characterized by behaviors that include one or more of the following: impaired control over drug use, compulsive use, continued use despite harm, and craving. Drug addiction is a treatable disease, utilizing a multidisciplinary approach, but relapse is common. "Drug-seeking" behavior is very common in addicts and drug abusers.

Abuse and addiction are separate and distinct from physical dependence and tolerance. Physicians should be aware that addiction may not be accompanied by concurrent tolerance and symptoms of physical dependence in all addicts. In addition, abuse of opioids can occur in the absence of addiction and is characterized by misuse for nonmedical purposes, often in combination with other psychoactive substances. Since SUBSYS may be diverted for non-medical use, careful record keeping of prescribing information, including quantity, frequency, and renewal requests is strongly advised.

Proper assessment of patients, proper prescribing practices, periodic re-evaluation of therapy, and proper dispensing and storage are appropriate measures that help to limit abuse of opioid drugs.

Handle SUBSYS appropriately to minimize the risk of diversion, including restriction of access and accounting procedures as appropriate to the clinical setting and as required by law.

Healthcare professionals should contact their State Professional Licensing Board, or State Controlled Substances Authority for information on how to prevent and detect abuse or diversion of this product.

9.3 Dependence

Opioid analgesics may cause physical dependence. Physical dependence results in withdrawal symptoms in patients who abruptly discontinue the drug. Withdrawal also may be precipitated through the administration of drugs with opioid antagonist activity, e.g., naloxone, nalmefene, or mixed agonist/antagonist analgesics (pentazocine, butorphanol, buprenorphine, nalbuphine).

Physical dependence usually does not occur to a clinically significant degree until after several weeks of continued opioid usage.

Tolerance, in which increasingly larger doses are required in order to produce the same degree of analgesia, is initially manifested by a shortened duration of analgesic effect, and subsequently, by decreases in the intensity of analgesia.

10 OVERDOSAGE

10.1 Clinical Presentation

The manifestations of SUBSYS overdose are expected to be similar in nature to intravenous fentanyl and other opioids, and are an extension of its pharmacological actions with the most serious significant effect being respiratory depression [see *Clinical Pharmacology* (12.2)].

10.2 Immediate Management

Immediate management of opioid overdose includes ensuring a patent airway, physical and verbal stimulation of the patient, and assessment of level of consciousness, ventilatory and circulatory status.

10.3 Treatment of Overdosage (Accidental Ingestion) in the Opioid NON-Tolerant Person

Provide ventilatory support, obtain intravenous access, and administer naloxone or other opioid antagonists as clinically indicated. The duration of respiratory depression following overdose may be longer than the effects of the opioid antagonist's action (e.g., the half-life of naloxone ranges from 30 to 81 minutes) and repeated administration may be necessary. Consult the package insert of the individual opioid antagonist for details about such use.

10.4 Treatment of Overdose in Opioid-Tolerant Patients

Provide ventilatory support and obtain intravenous access as clinically indicated. Judicious use of naloxone or another opioid antagonist may be warranted in some instances, but it is associated with the risk of precipitating an acute withdrawal syndrome.

10.5 General Considerations for Overdose

Management of SUBSYS overdose includes: securing a patent airway, assisting or controlling ventilation, establishing intravenous access. In the presence of respiratory depression or apnea, assist or control ventilation, and administer oxygen as indicated.

Carefully observe and appropriately manage overdosed patients until their clinical condition is well controlled.

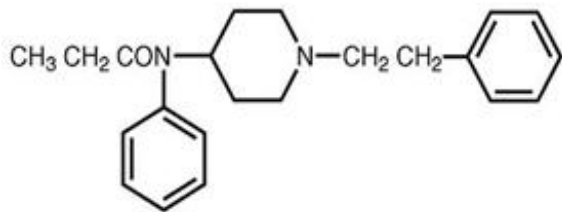
Although muscle rigidity interfering with respiration has not been seen following the use of SUBSYS, this is possible with fentanyl and other opioids. If it occurs, manage by the use of assisted or controlled ventilation, by the administration of an opioid antagonist, and, as a final alternative, by the administration of a neuromuscular blocking agent.

11 DESCRIPTION

SUBSYS (fentanyl sublingual spray) is a potent opioid analgesic intended for sublingual mucosal administration.

SUBSYS is formulated to be sprayed underneath the tongue to allow for absorption of fentanyl across the sublingual mucosa.

Active Ingredient: Fentanyl is N-phenyl-N-[1-(2-phenylethyl)-4-piperidinyl]propanamide. Fentanyl is a highly lipophilic compound (octanol-water partition coefficient at pH 7.4 is 860:1) that is freely soluble in ethanol and methanol and practically insoluble in water (1:40). The molecular weight of the free base is 336.47. The pKa is 8.4. The compound has the following structural formula:



Inactive Ingredients: dehydrated alcohol 63.6%, purified water, propylene glycol, xylitol, and L-menthol.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Fentanyl is an opioid agonist whose principal therapeutic action is analgesia. Other members of the class known as opioid agonists include substances such as morphine, oxycodone, hydromorphone, codeine, and hydrocodone.

12.2 Pharmacodynamics

Pharmacological effects of opioid agonists include anxiolysis, euphoria, feelings of relaxation, respiratory depression, constipation, miosis, cough suppression, and analgesia. Like all pure opioid agonist analgesics, with increasing doses there is increasing analgesia, unlike with mixed agonist/antagonists or non-opioid analgesics, where there is a limit to the analgesic effect with increasing doses.

With pure opioid agonist analgesics, there is no defined maximum dose; the ceiling to analgesic effectiveness is imposed only by side effects, the more serious of which may include somnolence and respiratory depression.

Analgesia

The analgesic effects of fentanyl are related to the blood level of the drug, if proper allowance is made for the delay into and out of the CNS (a process with a 3- to 5-minute half-life).

In general, the effective concentration and the concentration at which toxicity occurs increase with increasing tolerance with any and all opioids. The rate of development of tolerance varies widely among individuals. As a result, the dose of SUBSYS should be individually titrated to achieve the desired effect [*see Dosage and Administration (2.2)*].

Central Nervous System

The precise mechanism of the analgesic action is unknown although fentanyl is known to be a *mu*-opioid receptor agonist. Specific CNS opioid receptors for endogenous compounds with opioid-like activity have been identified throughout the brain and spinal cord and play a role in the analgesic effects of this drug.

Fentanyl produces respiratory depression by direct action on brain stem respiratory centers. The respiratory depression involves both a reduction in the responsiveness of the brain stem to increases in carbon dioxide and to electrical stimulation.

Fentanyl depresses the cough reflex by direct effect on the cough center in the medulla. Antitussive effects may occur with doses lower than those usually required for analgesia.

Fentanyl causes miosis even in total darkness. Pinpoint pupils are a sign of opioid overdose but are not pathognomonic (e.g., pontine lesions of hemorrhagic or ischemic origin may produce similar findings).

Gastrointestinal System

Fentanyl causes a reduction in motility associated with an increase in smooth muscle tone in the antrum of the stomach and in the duodenum. Digestion of food is delayed in the small intestine and propulsive contractions are decreased. Propulsive peristaltic waves in the colon are decreased, while tone may be increased to the point of spasm resulting in constipation. Other opioid-induced effects may include a reduction in gastric, biliary and pancreatic secretions, spasm of the sphincter of Oddi, and transient elevations in serum amylase.

Cardiovascular System

Fentanyl may produce release of histamine with or without associated peripheral vasodilation. Manifestations of histamine release and/or peripheral vasodilation may include pruritus, flushing, red eyes, sweating, and/or orthostatic hypotension.

Endocrine System

Opioid agonists have been shown to have a variety of effects on the secretion of hormones. Opioids inhibit the secretion of ACTH, cortisol, and luteinizing hormone (LH) in humans. They also stimulate prolactin, growth hormone (GH) secretion, and pancreatic secretion of insulin and glucagon in humans and other species, rats and dogs. Thyroid stimulating hormone (TSH) has been shown to be both inhibited and stimulated by opioids.

Respiratory System

All opioid *mu*-receptor agonists, including fentanyl, produce dose-dependent respiratory depression. The risk of respiratory depression is less in patients receiving chronic opioid therapy who develop tolerance to respiratory depression and other opioid effects. During the titration phase of the clinical trials, somnolence, which may be a precursor to respiratory depression, did increase in patients who were treated with higher doses of SUBSYS. Peak respiratory depressive effects may be seen as early as 15 to 30 minutes from the start of oral transmucosal fentanyl product administration and may persist for several hours.

Serious or fatal respiratory depression can occur even at recommended doses. Fentanyl depresses the cough reflex as a result of its CNS activity. Although not observed with oral transmucosal fentanyl products in clinical trials, fentanyl given rapidly by intravenous injection in large doses may interfere with respiration by causing rigidity in the muscles of respiration. Therefore, physicians and other healthcare providers should be aware of this potential complication [see *Boxed Warning - Warning: Importance Of Proper Patient Selection, Dosing, and Potential for Abuse, Contraindications (4), Warnings and Precautions (5.2), Adverse Reactions (6), and Overdosage (10)*].

12.3 Pharmacokinetics

Absorption

Following the single dose administration of SUBSYS, 400 mcg, the mean absolute bioavailability of fentanyl is 76% as measured by $AUC_{0-\infty}$. Fentanyl pharmacokinetic profile and bioavailability depend on the fraction of the dose that is absorbed through the sublingual mucosa and the fraction swallowed from the gastrointestinal tract.

In a study that compared the relative bioavailability of SUBSYS and oral transmucosal fentanyl citrate [OTFC] in 21 healthy adult subjects, the rate and extent of fentanyl absorption were considerably greater with SUBSYS [34% greater maximum plasma concentration (C_{max}) and 38% greater systemic exposure (AUC_{inf})] (Table 5 and Figure 1). [see *Dosage and Administration (2.1) and Warnings and Precautions (5.2)*].

Figure 1 includes an inset which shows the mean plasma concentration versus time profile to 4 hours.

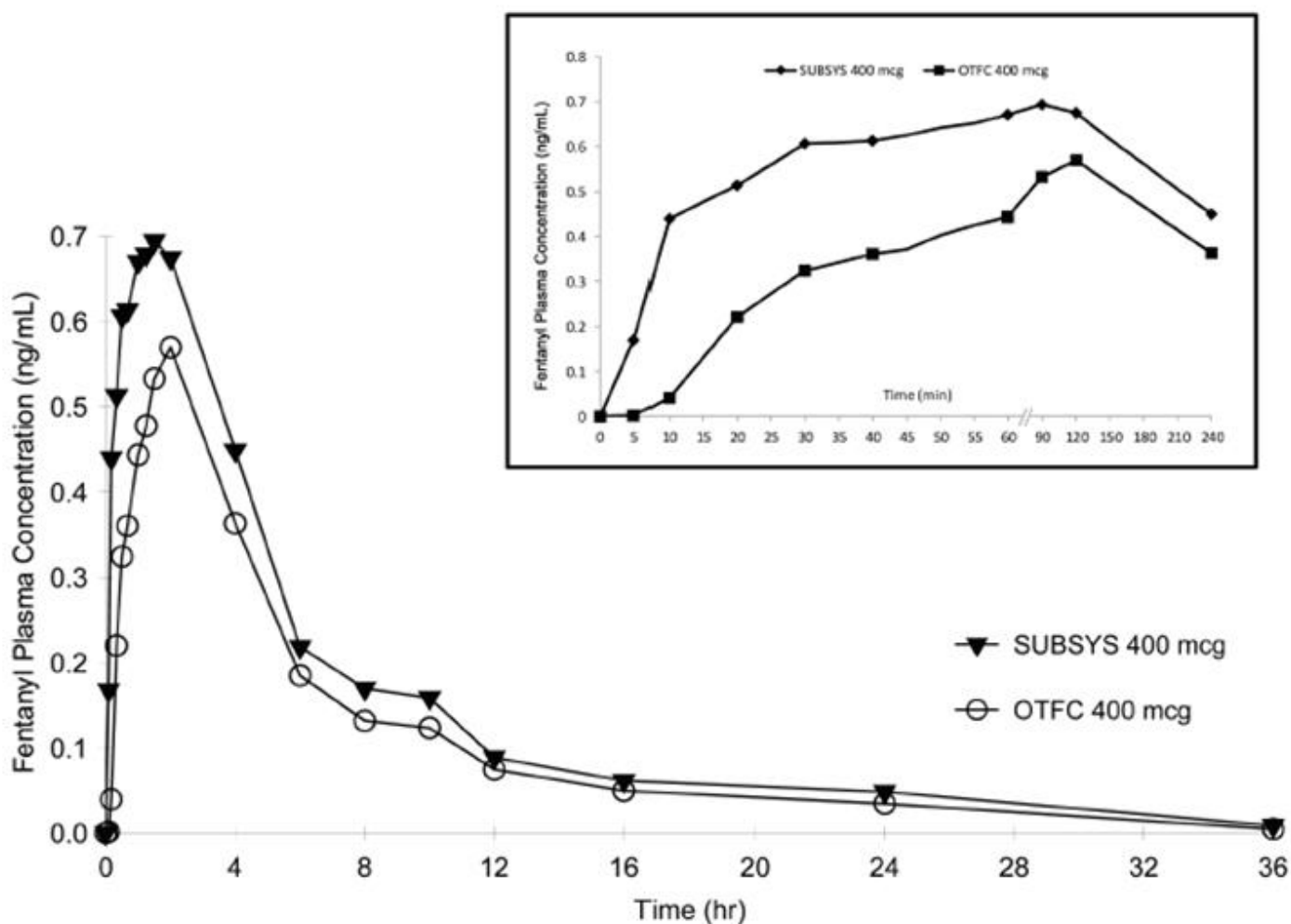
Table 5. Pharmacokinetic Parameters of Fentanyl in Healthy Adult Subjects Receiving a Single Dose of SUBSYS or OTFC

Pharmacokinetic Parameter (Mean (CV%))	SUBSYS 400 mcg	OTFC 400 mcg
T_{max} (hour)*	1.5 (0.17, 2.00)	2.0 (0.5, 2.12)
C_{max} (ng/mL)	0.813 (31.00)	0.607 (30.48)
AUC_{0-t} (ng/mL×hr)	4.863 (35.12)	3.677 (39.16)
$AUC_{0-\infty}$ (ng/mL×hr)	5.761 (33.26)	4.182 (39.93)

* Data for T_{max} presented as median (range)

Figure 1

Mean Fentanyl Plasma Concentration-Time Profiles Following Single Dose Administration of SUBSYS 400 mcg and OTFC 400 mcg in Healthy Adult Subjects

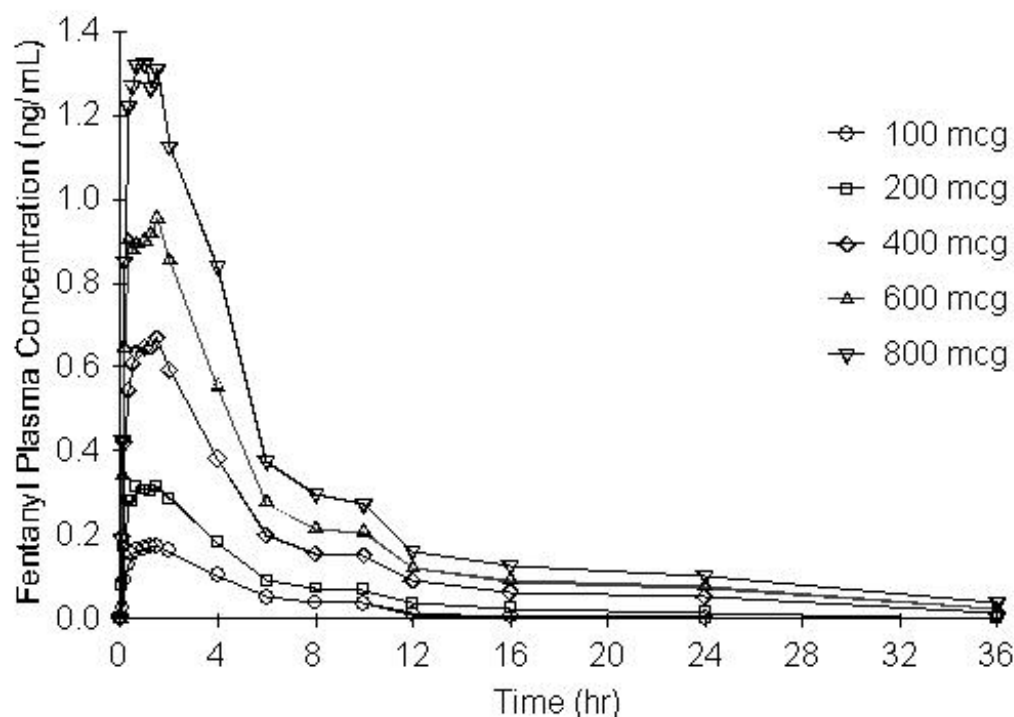


Neither peak fentanyl concentration nor total exposure was appreciably affected by the pretreatment of oral cavity with hot water or refrigerated iced water, low or high pH beverages when SUBSYS was administered under fasted condition.

Dose proportionality among the five available strengths of SUBSYS (100, 200, 400, 600, and 800 mcg) has been evaluated in a crossover study in healthy subjects. Mean plasma fentanyl levels following these five dose levels of SUBSYS are shown in Figure 2. The curves for each dose level are similar in shape with increasing dose levels producing increasing plasma fentanyl levels. The C_{max} and $AUC_{0-\infty}$ values increased in a dose-dependent manner that is approximately proportional to the SUBSYS doses administered.

Figure 2.

Mean Fentanyl Plasma Concentration-Time Profiles (36 hours) after Administration of SUBSYS 100 mcg, 200 mcg, 400 mcg, 600 mcg, and 800 mcg in Healthy Subjects



The pharmacokinetic parameters of the five strengths of SUBSYS tested are shown in Table 6. The mean C_{\max} ranged from 0.202 – 1.610 ng/mL. The median time of maximum plasma concentration (T_{\max}) across these five doses of SUBSYS varied from 0.67 - 1.25 hours (range of 0.08 – 4.00 hours) as measured after the start of administration.

Table 6. Fentanyl Plasma Pharmacokinetic Parameters in Healthy Adult Subjects Receiving Single Doses of 100, 200, 400, 600, 800 mcg of SUBSYS

Pharmacokinetic Parameter (Mean (% CV))	100 mcg	200 mcg	400 mcg	600 mcg	800 mcg
T_{\max} (hr)*	1.25 (0.17-2.05)	1.25 (0.17-2.03)	1.00 (0.17-2.03)	0.67 (0.08-2.00)	0.69 (0.17-4.00)
C_{\max} (ng/mL)	0.202 (28.35)	0.378 (29.69)	0.800 (27.66)	1.17 (32.48)	1.610 (37.22)
AUC_{last} (ng/mL×hr)	0.9776 (49.82)	1.985 (40.93)	4.643 (44.53)	6.682 (32.46)	9.450 (36.62)
$AUC_{0-\infty}$ (ng/mL×hr)	1.245 (53.82)	2.475 (46.48)	5.342 (44.16)	7.446 (81.54)	10.38 (35.60)
$T_{1/2}$ (hr)	5.25 (89.92)	8.45 (77.94)	11.03 (62.20)	10.64 (41.73)	11.99 (32.15)

* Data for T_{\max} presented as median (range)

The effect of mucositis (Grades 1 and 2) on the pharmacokinetics of SUBSYS was studied in a group of cancer patients with mucositis (N = 7 for Grade 1 and N = 2 for Grade 2) and without mucositis (N = 8). A single 100 mcg dose was administered. Mean summary statistics (standard deviation in parentheses)

for patients with Grade 1 mucositis and patients without mucositis are presented in Table 7. Cancer patients with Grade 1 mucositis exhibited 73% greater C_{\max} and 52% greater AUC_{last} values in comparison to patients without mucositis. The two cancer patients with Grade 2 mucositis had 4- and 7-fold higher C_{\max} and ≥ 3 - fold higher AUC_{last} values compared to patients without mucositis.

Monitor patients with Grade 1 mucositis closely for signs of respiratory and central nervous system depression particularly during initiation of therapy with SUBSYS. As a result of the large and variable increase in exposure of fentanyl, use of SUBSYS should be avoided in patients with Grade 2 and more severe mucositis unless the benefits are expected to outweigh the risk of respiratory depression.

Table 7. Mean (% CV) Pharmacokinetic Parameters in Patients with Mucositis

Patient Status	N	C_{\max} (ng/mL)	T_{\max} (hr)*	$AUC_{0-\text{last}}$ (ng/mL×hr)
Mucositis Grade 1	7	0.45 (95.56)	0.25 (0.25, 2.00)	1.38 (44.93)
No Mucositis	8	0.26 (57.69)	0.38 (0.25, 2.00)	0.91 (14.29)

* Data for T_{\max} presented as median (range)

Distribution

Fentanyl is highly lipophilic. Animal data showed that following absorption, fentanyl is rapidly distributed to the brain, heart, lungs, kidneys and spleen followed by a slower redistribution to muscles and fat. The plasma protein binding of fentanyl is 80-85%. The main binding protein is alpha-1-acid glycoprotein, but both albumin and lipoproteins contribute to some extent. The free fraction of fentanyl increases with acidosis. The mean volume of distribution at steady state (V_{ss}) was 4 L/kg.

Metabolism

Fentanyl is metabolized in the liver and in the intestinal mucosa to norfentanyl by cytochrome P450 3A4 isoform. Norfentanyl was not found to be pharmacologically active in animal studies [see *Drug Interactions (7)*].

Elimination

Fentanyl is primarily (more than 90%) eliminated by biotransformation to N-dealkylated and hydroxylated inactive metabolites. Less than 7% of the dose is excreted unchanged in the urine, and only about 1% is excreted unchanged in the feces. The metabolites are mainly excreted in the urine, while fecal excretion is less important. The total plasma clearance of fentanyl was 0.5 L/hr/kg (range 0.3 - 0.7 L/hr/kg). The terminal half-life after SUBSYS administration is from 5 to 12 hours.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies in animals have not been performed to evaluate the carcinogenic potential of fentanyl.

Fentanyl citrate was not mutagenic in the *in vitro* Ames reverse mutation assay in *S. typhimurium* or *E. coli* or the mouse lymphoma mutagenesis assay, and was not clastogenic in the *in vivo* mouse micronucleus assay.

Fentanyl has been shown to impair fertility in rats at doses of 30 mcg/kg intravenously and 160 mcg/kg subcutaneously. Conversion to the human equivalent doses indicates that this is within the range of the human recommended dosing for SUBSYS.

14 CLINICAL STUDIES

The efficacy of SUBSYS was demonstrated in a double-blind, placebo-controlled, crossover study in

opioid tolerant adult patients with cancer and breakthrough pain. The dose range studied was from 100 mcg per dose to 1600 mcg per dose. Patients entering the trial must have had on average 1-4 episodes of pain per day not controlled on stable, chronic maintenance doses of opioid medication of at least 60 mg/day of morphine, 25 mcg/hr of transdermal fentanyl, or an equianalgesic dose of another opioid for at least 7 days.

The study began with an open-label dose titration period followed by a double-blind treatment period. The goal of titration was to find the dose of SUBSYS that provided adequate analgesia with acceptable side effects. Patients were titrated from a 100 mcg starting dose. Once a successful dose was established, patients were enrolled into the double-blind period and randomized to a sequence of 10 treatments; 7 with SUBSYS and 3 with placebo.

Patients assessed pain intensity on a 100 mm visual analog scale that rated the pain as 0=none to 100=worst possible pain. With each episode of breakthrough pain, pain intensity was assessed first and then treatment was administered. Pain intensity (0-100) was then measured at 5, 10, 15, 30, 45 and 60 minutes after the start of administration. The summed pain intensity difference from baseline to 30 minutes after dosing was the primary efficacy measure.

Out of 130 patients who entered the titration phase, 98 (75%) were able to titrate to a dose that adequately reduced pain with tolerable side effects and entered into the double-blind period.

The breakdown of successful dose for the patients entering the double-blind period of the study is as follows:

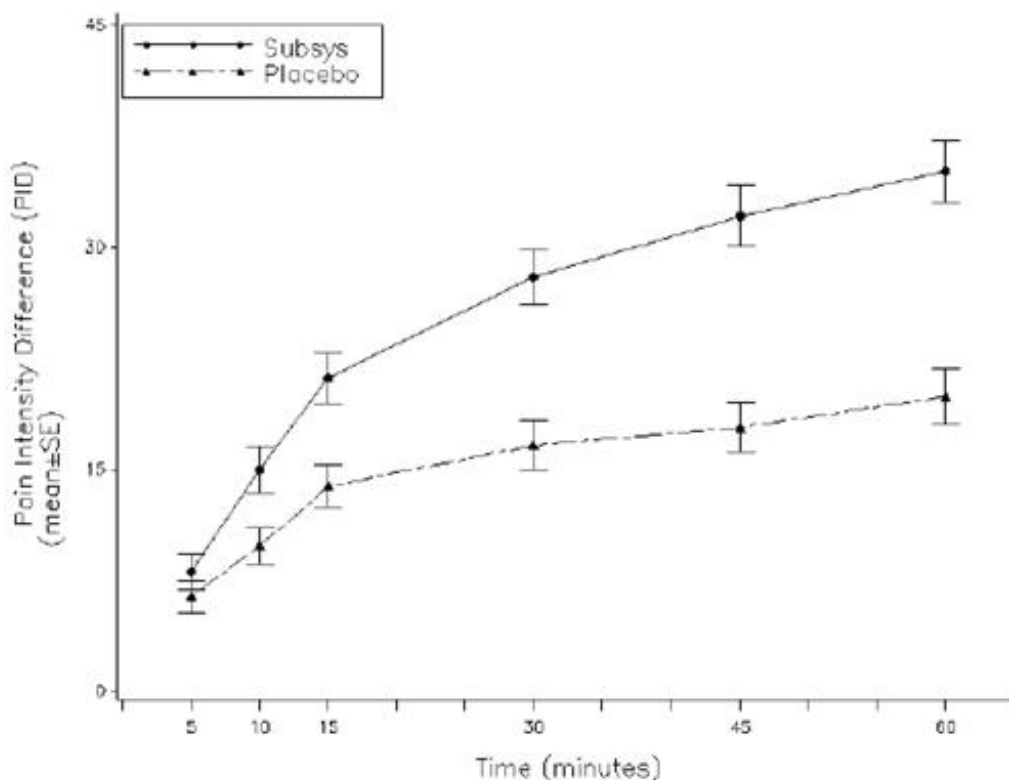
SUBSYS Dose	Total No. (%) n=96
100 mcg	4 (4%)
200 mcg	7 (7%)
400 mcg	14 (15%)
600 mcg	15 (16%)
800 mcg	23 (24%)
1200 mcg (2 × 600 mcg)	20 (21%)
1600 mcg (2 × 800 mcg)	13 (14%)

SUBSYS produced a statistically significantly greater reduction in pain intensity compared to placebo as measured by the Summed Pain Intensity Differences scale (SPID) at 30 minutes.

The primary outcome measure, the mean sum of the pain intensity difference at 30 minutes (SPID30), was statistically significantly higher for SUBSYS than for placebo. The difference in mean pain intensity based on a 100 mm visual analog scale is displayed in Figure 3.

Figure 3

Pain Intensity Differences over Time



16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 Storage and Handling

SUBSYS is supplied in individually sealed blister packages. Store at 20-25°C (68-77°F) with excursions permitted between 15° and 30°C (59° to 86°F) until ready to use. [See USP Controlled Room Temperature.] Do not use if the blister package has been opened.

16.2 Disposal of SUBSYS

Patients and caregivers must be advised to dispose of used unit dose systems immediately after use and any unneeded unit dose systems remaining from a prescription as soon as they are no longer needed. Consumed units represent a special risk because they are no longer protected by the blister package, yet may contain enough medicine to be fatal to a child. [see *Patient Counseling Information (17)*].

Charcoal-lined disposal pouches are provided with every carton dispensed. [see *Patient Counseling Information (17)*]. A charcoal-lined disposal pouch is to be used by patients or their caregivers to dispose of the contents of any unneeded unit dose systems when they are no longer needed. Instructions for usage of the disposal pouch are included in the *Medication Guide*.

Patients and members of their household must be advised to dispose of any units remaining from a prescription as soon as they are no longer needed.

Instructions for disposal are also included in *Disposal of Used SUBSYS Unit Dose Systems (17)* and *Disposal of Unopened SUBSYS Unit Dose Systems When No Longer Needed (17)* and in the *Medication Guide*. If additional assistance is required, call Insys Therapeutics, Inc. at 1-877-978-2797.

16.3 How Supplied

Each SUBSYS carton contains individual blister packages containing spray units of SUBSYS, a supply of small white disposal bags for disposing of used SUBSYS units and charcoal-lined disposal pouches, a supply of charcoal-lined disposal pouches (wrapped in aluminum foil) for use when disposing of the contents of unused SUBSYS units, a Medication Guide and a Package Insert.

SUBSYS is supplied in individually sealed, protective blister packages. These blister packages are packed into 10 and 30 per shelf cartons.

Each unit dose system consists of a white actuator attached to a light purple vial holder. The dosage strength is marked on the label on the actuator, the blister package and the shelf carton. See the protective blister package and shelf carton for product information.

Dosage Strength (fentanyl base)	Carton/Blister Package Color	NDC Number
100 mcg	Blue	20482-001-10
		20482-001-30
200 mcg	Green	20482-002-10
		20482-002-30
400 mcg	Magenta (Pink)	20482-004-10
		20482-004-30
600 mcg	Purple	20482-006-10
		20482-006-30
800 mcg	Orange	20482-008-10
		20482-008-30
1200 mcg	Brown	20482-012-15
1600 mcg	Red	20482-016-15

Note: Colors are a secondary aid in product identification. Please be sure to confirm the printed dosage before dispensing.

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (*Medication Guide*).

Patient/Caregiver Instructions

Before initiating treatment with SUBSYS, explain the statements below to patients and/or caregivers. Instruct patients to read the Medication Guide each time SUBSYS is dispensed because new information may be available.

- Outpatients must be enrolled in the TIRF REMS Access program before they can receive SUBSYS.
- Allow patients the opportunity to ask questions and discuss any concerns regarding SUBSYS or the TIRF REMS Access program.
- As a component of the TIRF REMS Access program, prescribers must review the contents of the SUBSYS Medication Guide with every patient before initiating treatment with SUBSYS.
- Advise the patient that SUBSYS is available only from pharmacies that are enrolled in the TIRF REMS Access program, and provide them with the telephone number and website for information on how to obtain the drug.
- Advise the patient that only enrolled healthcare providers may prescribe SUBSYS.
- Patient must sign the Patient-Prescriber Agreement to acknowledge that they understand the risks of SUBSYS.
- Advise patients that they may be requested to participate in a survey to evaluate the effectiveness of the TIRF REMS Access program.

1. **Patients and their caregivers must be instructed that children exposed to SUBSYS are at high risk OF FATAL RESPIRATORY DEPRESSION.** Patients and their caregivers must be instructed to keep SUBSYS out of the reach of children [*See How Supplied/Storage and Handling (16.1), Warnings and Precautions (5.2 and 5.3) and Medication Guide for specific patient instructions.*]
2. Provide patients and their caregivers with a *Medication Guide* each time SUBSYS is dispensed

because new information may be available.

3. Instruct patients and their caregivers to keep both used and unused dosage units out of the reach of children. Consumed units must be properly disposed of as soon as possible [*see How Supplied/Storage and Handling (16.1), Warnings and Precautions (5.3), and Patient Counseling Information (17)*].
4. Instruct patients not to take SUBSYS for acute pain, postoperative pain, pain from injuries, headache, migraine or any other short-term pain, even if they have taken other opioid analgesics for these conditions.
5. Instruct patients on the meaning of opioid tolerance and that SUBSYS is only to be used as a supplemental pain medication for patients with pain requiring around-the-clock opioids, who have developed tolerance to the opioid medication, and who need additional opioid treatment of breakthrough pain episodes.
6. Instruct patients that, if they are not taking an opioid medication on a scheduled basis (around-the-clock), they should not take SUBSYS.
7. Instruct patients that, if the breakthrough pain episode is not relieved 30 minutes after administration, they may take **ONLY ONE ADDITIONAL DOSE OF SUBSYS USING THE SAME STRENGTH FOR THAT EPISODE. Thus, patients should take no more than two doses of SUBSYS for any breakthrough pain episode.**
8. Instruct patients that they **MUST** wait at least 4 hours before treating another episode of breakthrough pain with SUBSYS.
9. Instruct patients **NOT** to share SUBSYS and that sharing SUBSYS with anyone else could result in the other individual's death due to overdose.
10. Make patients aware that SUBSYS contains fentanyl which is a strong pain medication similar to hydromorphone, methadone, morphine, oxycodone, and oxymorphone.
11. Instruct patients that the active ingredient in SUBSYS, fentanyl, is a drug that some people abuse. SUBSYS should be taken only by the patient it was prescribed for, and it should be protected from theft or misuse in the work or home environment.
12. Caution patients to talk to their doctor if breakthrough pain is not alleviated or worsens after taking SUBSYS.
13. Instruct patients to use SUBSYS exactly as prescribed by their doctor and not to take SUBSYS more often than prescribed.
14. Caution patients that SUBSYS can affect a person's ability to perform activities that require a high level of attention (such as driving or using heavy machinery). Warn patients taking SUBSYS of these dangers and counsel them accordingly.
15. Warn patients to not combine SUBSYS with alcohol, sleep aids, or tranquilizers except by the orders of the prescribing physician, because dangerous additive effects may occur, resulting in serious injury or death.
16. Inform female patients that if they become pregnant or plan to become pregnant during treatment with SUBSYS, they should ask their doctor about the effects that SUBSYS (or any medicine) may have on them and their unborn children.

SUBSYS Child Safety Kit

Provide patients and their caregivers with a SUBSYS Child Safety Kit. The kit consists of a portable carrying case, a lock for the bag and contains a package of cabinet and drawer child safety latches for securing the storage space at home to help patients store SUBSYS and other medicines out of the reach of children. To obtain a supply of Child Safety Kits, health care professionals can call Insys Therapeutics, Inc., at 1-877-978-2797.

Disposal of Used SUBSYS Unit Dose Systems

Patients must be instructed to safely dispose of used SUBSYS units.

1. After administration of SUBSYS, place the used spray unit into one of the disposable bags provided with your prescription.

2. Seal the bag and discard into a trash container out of the reach of children.

Disposal of Unopened SUBSYS Unit Dose Systems When No Longer Needed

Patients and members of their household must be advised to dispose of any unopened units remaining from a prescription as soon as they are no longer needed.

To dispose of the unopened SUBSYS units:

1. Using a pair of scissors, cut the blister package on the line marked by an image of a pair of scissors and the instruction "cut to open" printed on the blister. Peel back the blister material to remove the SUBSYS unit from the package.
2. Remove a charcoal-lined disposal pouch from the aluminum foil package by tearing open the package at the notch.
3. Hold the charcoal-lined disposal pouch with the opening facing up. Put the nozzle of the SUBSYS spray unit upside-down into the opening of the charcoal-lined disposal pouch.
4. Squeeze your fingers and thumb together to spray SUBSYS into the charcoal-lined disposal pouch.
5. Dispose of the empty spray unit in a disposal bag.
6. Repeat the above steps for each unused SUBSYS spray unit. The charcoal-lined disposal pouch may be used for disposing of the contents of up to 10 spray units. Make sure all unused spray units have been sprayed into a charcoal-lined disposal pouch.
7. To seal the used charcoal-lined disposal pouch, remove the backing from the adhesive strip. Fold the flap down and press to seal the charcoal-lined disposal pouch.
8. Place the sealed charcoal-lined disposal pouch into a disposal bag.
9. To seal the disposal bag, remove the backing from the adhesive strip. Fold the flap down and press to seal.
10. Discard the sealed disposal bag in the trash out of the reach of children.

Detailed instructions for the proper storage, administration, disposal, and important instructions for managing an overdose of SUBSYS are provided in the *SUBSYS Medication Guide*. Encourage patients to read this information in its entirety and give them an opportunity to have their questions answered.

In the event that a caregiver requires additional assistance in disposing of excess unusable units that remain in the home after a patient has expired, instruct them to call the toll-free number for Insys Therapeutics, Inc. (1-877-978-2797) or seek assistance from their local DEA office.

U.S. Patents: 8,486,972 B2 and 8,486,973 B2

122414

SUBSYS® is a registered trademark of INSYS Therapeutics, Inc.

Medication Guide

SUBSYS® (sub sis) CII

(fentanyl)

sublingual spray

100 mcg, 200 mcg, 400 mcg, 600 mcg, 800 mcg

IMPORTANT:

Do not use SUBSYS unless you are regularly using another opioid pain medicine around-the-clock for your cancer pain and your body is used to these medicines (this means that you are opioid tolerant). You can ask your healthcare provider if you are opioid tolerant.

Keep SUBSYS in a safe place away from children.

Get emergency medical help right away if:

- **a child uses SUBSYS. SUBSYS can cause an overdose and death in any child who uses it.**
- **an adult who has not been prescribed SUBSYS uses it**
- **an adult who is not already taking opioids around-the-clock, uses SUBSYS**

These are medical emergencies that can cause death.

Read this Medication Guide completely before you start using SUBSYS, and each time you get a new prescription. There may be new information. This Medication Guide does not take the place of talking to your healthcare provider about your medical condition or your treatment. Be sure to share this important information with members of your household and other caregivers.

What is the most important information I should know about SUBSYS?

SUBSYS can cause life-threatening breathing problems which can lead to death.

1. **Do not take SUBSYS if you are not opioid tolerant.**
2. If you stop taking your around-the-clock opioid pain medicine for your cancer pain, **you must stop using SUBSYS.** You may no longer be opioid tolerant. Talk to your healthcare provider about how to treat your pain.
3. **Use SUBSYS exactly as prescribed by your healthcare provider.**
 - You must not use more than 2 doses of SUBSYS for each episode of breakthrough cancer pain.
 - You must wait four hours before treating a new episode of breakthrough pain with SUBSYS.**See the Medication Guide section "How should I use SUBSYS?" and the "Instructions for Use" section at the end of this Medication Guide for detailed information about how to use SUBSYS the right way.**
4. **Do not switch from SUBSYS to other medicines that contain fentanyl without talking with your healthcare provider.** The amount of fentanyl in a dose of SUBSYS is not the same as the amount of fentanyl in other medicines that contain fentanyl. Your healthcare provider will prescribe a starting dose of SUBSYS that may be different than other fentanyl containing medicines you may have been taking.
5. **Do not** use SUBSYS for short-term pain that you would expect to go away in a few days, such as:
 - pain after surgery
 - headache or migraine
 - dental pain
6. **Never give SUBSYS to anyone else**, even if they have the same symptoms you have. It may harm them or even cause death.

SUBSYS is a federally controlled substance (CII) because it is a strong opioid (narcotic) pain medicine that can be misused by people who abuse prescription medicines or street drugs.

- **Prevent theft, misuse or abuse. Keep SUBSYS in a safe place** to protect it from being stolen. SUBSYS can be a target for people who abuse opioid (narcotic) medicines or street drugs.
- **Selling or giving away this medicine is against the law.**

SUBSYS is available only through a program called the TIRF REMS ACCESS program. To receive SUBSYS, you must:

- talk to your healthcare provider

- understand the benefits and risks of SUBSYS
- agree to all of the instructions
- sign the Patient-Prescriber Agreement form

What is SUBSYS?

- SUBSYS is a prescription medicine that contains the medicine fentanyl.
- SUBSYS is used to manage breakthrough pain in adults with cancer, who are already routinely taking other opioid pain medicines around-the-clock for cancer pain.
- SUBSYS is started only after you have been taking other opioid pain medicines and your body has become used to them (you are opioid tolerant). Do not use SUBSYS if you are not opioid tolerant.
- You must stay under your healthcare provider's care while taking SUBSYS.
- SUBSYS is a liquid medicine that is sprayed underneath your tongue (sublingual) and allowed to absorb.
- SUBSYS is only:
 - available through the TIRF REMS ACCESS program
 - given to people who are opioid tolerant

It is not known if SUBSYS is safe and effective in children under 18 years of age.

Who should not use SUBSYS?

Do not use SUBSYS:

- **if you are not opioid tolerant. Opioid tolerant means that you are already taking other opioid pain medicines around-the-clock for your cancer pain, and your body is used to these medicines.**
- for short-term pain that you would expect to go away in a few days, such as:
 - pain after surgery
 - headache or migraine
 - dental pain
- if you are allergic to any of the ingredients in SUBSYS. See the end of this Medication Guide for a complete list of other ingredients in SUBSYS.

What should I tell my healthcare provider before using SUBSYS?

Before using SUBSYS, tell your healthcare provider if you:

- have sores or ulcers in your mouth
- have trouble breathing or lung problems such as asthma, wheezing, or shortness of breath
- have or had a head injury or brain problem
- have liver or kidney problems
- have seizures
- have a slow heart rate or other heart problems
- have low blood pressure
- have mental health problems including major depression, schizophrenia or hallucinations (seeing or hearing things that are not there)
- have a past or present drinking problem (alcoholism), or a family history of drinking problems
- have a past or present drug abuse problem or addiction problem, or a family history of a drug abuse problem or addiction problem
- have any other medical conditions
- are pregnant or plan to become pregnant. SUBSYS may cause serious harm to your unborn baby.
- are breastfeeding or plan to breastfeed. SUBSYS can pass into your breast milk. It can cause serious harm to your baby. You should not use SUBSYS while breastfeeding.

Tell your healthcare provider about all the medicines you take, including prescription and non-

prescription medicines, vitamins, and herbal supplements. Some medicines may cause serious or life-threatening side effects when taken with SUBSYS. Sometimes, the doses of certain medicines and SUBSYS may need to be changed if used together.

- **Do not take any medicine while using SUBSYS until you have talked to your healthcare provider.** Your healthcare provider will tell you if it is safe to take other medicines while you are using SUBSYS.
- Be very careful about taking other medicines that may make you sleepy, such as other pain medicines, anti-depressants, sleeping pills, anti-anxiety medicines, antihistamines, muscle relaxants or tranquilizers.

Know the medicines you take. Keep a list of them to show your healthcare provider and pharmacist when you get a new medicine.

How should I use SUBSYS?

Before you can begin to use SUBSYS:

- Your healthcare provider will explain the TIRF REMS ACCESS program to you.
- You will sign the TIRF REMS ACCESS program Patient-Prescriber Agreement form.
- SUBSYS is only available at pharmacies that are part of the TIRF REMS ACCESS program. Your healthcare provider will let you know the pharmacy closest to your home where you can have your SUBSYS prescription filled.

Using SUBSYS:

- **Use SUBSYS exactly as prescribed.** Do not use SUBSYS more often than prescribed.
- See the "Instructions for Use" section at the end of this Medication Guide for detailed information about the right way to use and throw away (dispose of) SUBSYS.
- SUBSYS comes in several strengths. When you are first prescribed SUBSYS, your healthcare provider will start you with the lowest strength medicine, and will change the dose until you and your healthcare provider find the right dose for you. **Do not change your dose of SUBSYS unless your healthcare provider tells you to. Each SUBSYS unit contains enough medicine for 1 spray.**
- **As your dose is adjusted, your healthcare provider will tell you whether your dose of SUBSYS is 1 or 2 sprays given underneath the tongue.**
 - **If your dose of SUBSYS is 1 spray, then you will use 1 SUBSYS unit for each dose.**
 - **If your dose of SUBSYS is 2 sprays, then you will use 2 SUBSYS units for each dose.**
- **Take 1 dose** of SUBSYS when you get an episode of breakthrough cancer pain.
- **Wait 30 minutes.** If you are still in pain after 30 minutes, **take 1 more dose** of SUBSYS as instructed by your healthcare provider.
- **Do not** take more than 2 doses of SUBSYS for an episode of breakthrough cancer pain. If your breakthrough pain does not get better after the second dose of SUBSYS, call your healthcare provider for instructions. **Do not use another dose of SUBSYS at this time.**
- **Wait at least 4 hours** before treating a new episode of breakthrough cancer pain with SUBSYS.
- Keep taking your around-the-clock opioid pain medicine while taking SUBSYS.
- If you have **more than 4 episodes of breakthrough cancer pain in a day**, talk to your healthcare provider. The dose of your around-the-clock opioid pain medicine may need to be adjusted.
- **If you use too much SUBSYS or overdose**, you or your caregiver should call for emergency medical help or have someone take you to the nearest hospital emergency room right away.

What should I avoid while using SUBSYS?

- **Do not drive, operate heavy machinery, or do other dangerous** activities until you know how SUBSYS affects you. SUBSYS can make you sleepy. Ask your healthcare provider when it is okay to do these activities.
- **Do not drink alcohol while using SUBSYS.** It can increase your chance of getting dangerous side

effects.

What are the possible side effects of SUBSYS?

SUBSYS can cause serious side effects, including:

1. **Breathing problems that can become life-threatening.** See "What is the most important information I should know about SUBSYS?"
 - **Call your healthcare provider or get emergency medical help right away if you:**
 - have trouble breathing
 - have drowsiness with slowed breathing
 - have shallow breathing (little chest movement with breathing)
 - feel faint, very dizzy, confused, or have other unusual symptoms

These symptoms can be a sign that you have used too much SUBSYS or the dose is too high for you. These symptoms may lead to serious problems or death if not treated right away. If you have any of these symptoms, do not use any more SUBSYS until you have talked to your healthcare provider.
2. **Decreased blood pressure.** This can make you feel dizzy or lightheaded if you get up too fast from sitting or lying down.
3. **Physical dependence. Do not stop using SUBSYS or any other opioid, without talking to your healthcare provider.** You could become sick with withdrawal symptoms because your body has become used to these medicines. Physical dependency is not the same as drug addiction.
4. **A chance of abuse or addiction.** This chance is higher if you are or have ever been addicted to or abused other medicines, street drugs, or alcohol, or if you have a history of mental health problems.

The most common side effects of SUBSYS are:

- nausea
- vomiting
- shortness of breath
- sleepiness
- dizziness
- headache

Constipation (not often enough or hard bowel movements) is a very common side effect of pain medicines (opioids) including SUBSYS and is unlikely to go away without treatment. Talk to your healthcare provider about dietary changes, and the use of laxatives (medicines to treat constipation) and stool softeners to prevent or treat constipation while using SUBSYS.

Tell your healthcare provider if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of SUBSYS. For more information, ask your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store SUBSYS?

- **Always keep SUBSYS in a safe place away from children and from anyone for whom it has not been prescribed.** Protect SUBSYS from theft.
- Store SUBSYS at room temperature, 68°F to 77°F (20°C to 25°C) until ready to use.
- Keep SUBSYS in the original blister package. Do not remove SUBSYS units from the blister packages for storage in a temporary container.
- See the "Instructions for Use" section at the end of this Medication Guide for information about the right way to dispose of SUBSYS when no longer needed.
- Use the SUBSYS Child Safety Kit to help you store SUBSYS and your other medicines out of the reach of children. It is very important that you use the items in the SUBSYS Child Safety Kit to help

protect the children in your home or visiting your home.

- Call Insys Therapeutics, Inc. at 1-877-978-2797 or visit www.subsyspray.com for a SUBSYS Child Safety Kit.

The SUBSYS Child Safety Kit contains important information on the storage and handling of SUBSYS.

The SUBSYS Child Safety Kit includes:

- a **portable carrying case (see Figure A)** and **lock (see Figure B)** for you to keep a small supply of SUBSYS. Keep the rest of your SUBSYS in the locked storage space.



Figure A

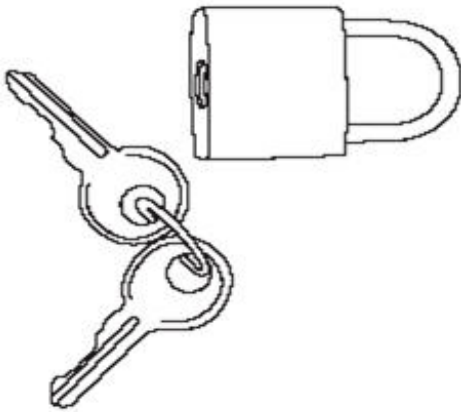


Figure B

- a **package of cabinet and drawer child safety latches (see Figure C)** to secure the storage space where SUBSYS is kept at home.

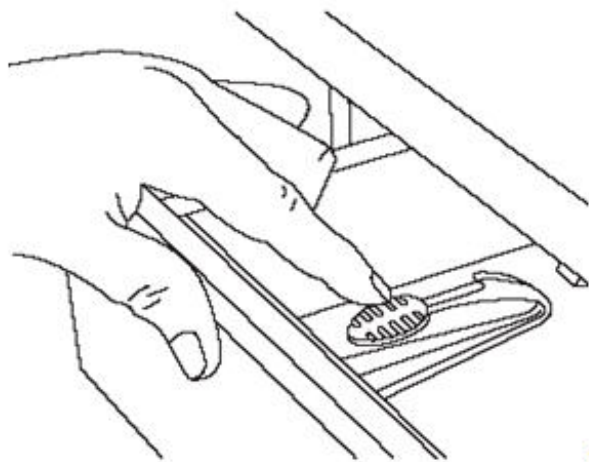


Figure C

- Keep the carrying case locked and away from children. (See Figure C)

General information about SUBSYS

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. **Use SUBSYS only for the purpose for which it was prescribed. Do not give SUBSYS to other people, even if they have the same symptoms you have.** SUBSYS can harm other people and even cause death. Sharing SUBSYS is against the law.

This Medication Guide summarizes the most important information about SUBSYS. If you would like more information, talk with your healthcare provider or pharmacist. You can ask your pharmacist or healthcare provider for information about SUBSYS that is written for healthcare professionals.

For more information about the TIRF REMS ACCESS program, go to www.TIRFREMSaccess.com or call 1-866-822-1483.

What are the ingredients in SUBSYS?

Active ingredient: fentanyl

Inactive ingredients: dehydrated alcohol 63.6%, purified water, propylene glycol, xylitol, and L-menthol.

Instructions for Use

Before you use SUBSYS, it is important that you read the Medication Guide and these Instructions for Use. Be sure that you read, understand, and follow these Instructions for Use so that you use SUBSYS the right way. Ask your healthcare provider or pharmacist if you have questions about the right way to use SUBSYS.

What will I find in the SUBSYS package?

Each SUBSYS Carton contains (See Figure D):

- individual blister packages containing spray units of SUBSYS
- a supply of small white disposal bags for use when disposing of used SUBSYS units and charcoal-lined disposal pouches
- a supply of charcoal-lined disposal pouches (wrapped in aluminum foil) for use when disposing of the contents of unused SUBSYS units
 - ***Call Insys Therapeutics, Inc. at 1-877-978-2797 for additional supplies of disposal bags and charcoal-lined disposal pouches.***
- a Medication Guide (not shown)
- a Package Insert (not shown)

- When you get an episode of breakthrough cancer pain, take the dose prescribed by your healthcare provider as follows: SUBSYS comes in individual blister packages. Do not open the blister package until you are ready to use it.

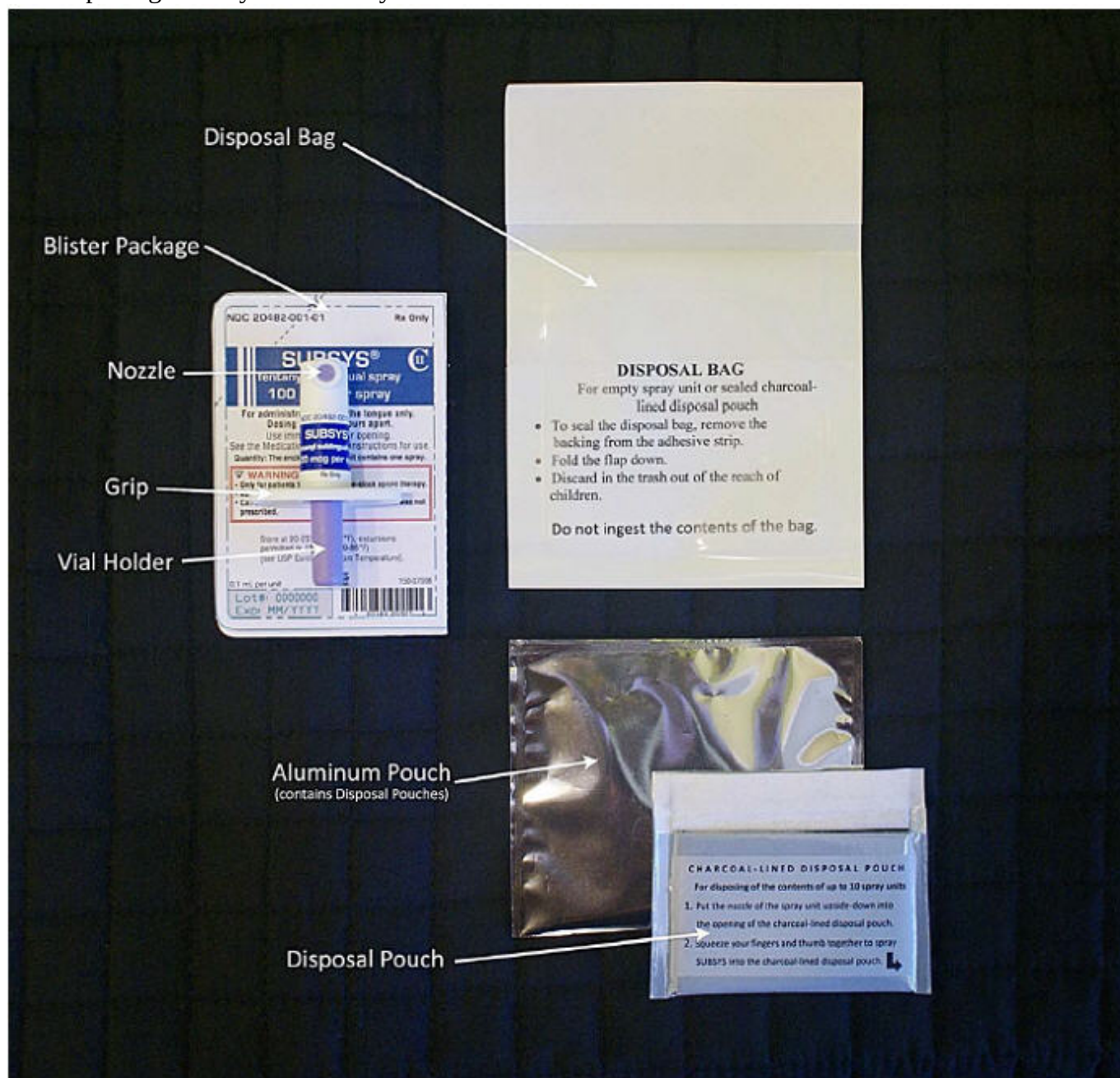


Figure D

- Remove the SUBSYS spray unit from the blister package by cutting the dashed line with a pair of scissors. (See Figure E)



Figure E

- To correctly use SUBSYS:
 - Swallow any saliva in your mouth.
 - Hold the SUBSYS spray unit **upright** using your index and middle fingers and thumb. (See **Figure F**)

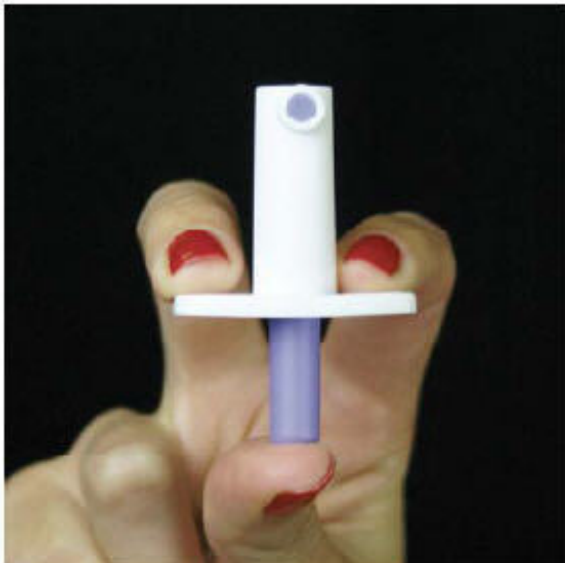


Figure F

- Point the nozzle **into** your mouth and **under** your tongue. (See **Figures G and H**)



Figure G



Figure H

- Squeeze your fingers and thumb together to spray SUBSYS under your tongue. **(See Figure I)**
- Hold the medicine under your tongue for **30-60 seconds**. Do not spit out any medicine. Do not rinse your mouth.



Figure I

- The SUBSYS spray unit will remain locked after use. **(See Figure J)**



Figure J

Disposing of SUBSYS:

After using SUBSYS, dispose of the spray unit as follows:

- Place the used SUBSYS spray unit into one of the disposal bags provided in the carton containing the spray units. **(See Figure K)**



Figure K

- Remove the backing from the adhesive strip.
- Fold the flap to seal the bag. **(See Figure L)**



Figure L

- Discard in the trash out of the reach of children. **(See Figure M)**



Figure M

Do not ingest the contents of the bag.

Disposal of any unused SUBSYS when no longer needed:

Before you throw away the SUBSYS spray units, you must empty all of the medicine into the charcoal-lined disposal pouch. This protects others, especially children from harm. ***Charcoal-lined disposal pouches are supplied wrapped in an aluminum foil package.***

- Remove a charcoal-lined disposal pouch from the aluminum foil package by tearing open the package at the notch. (See Figures N)

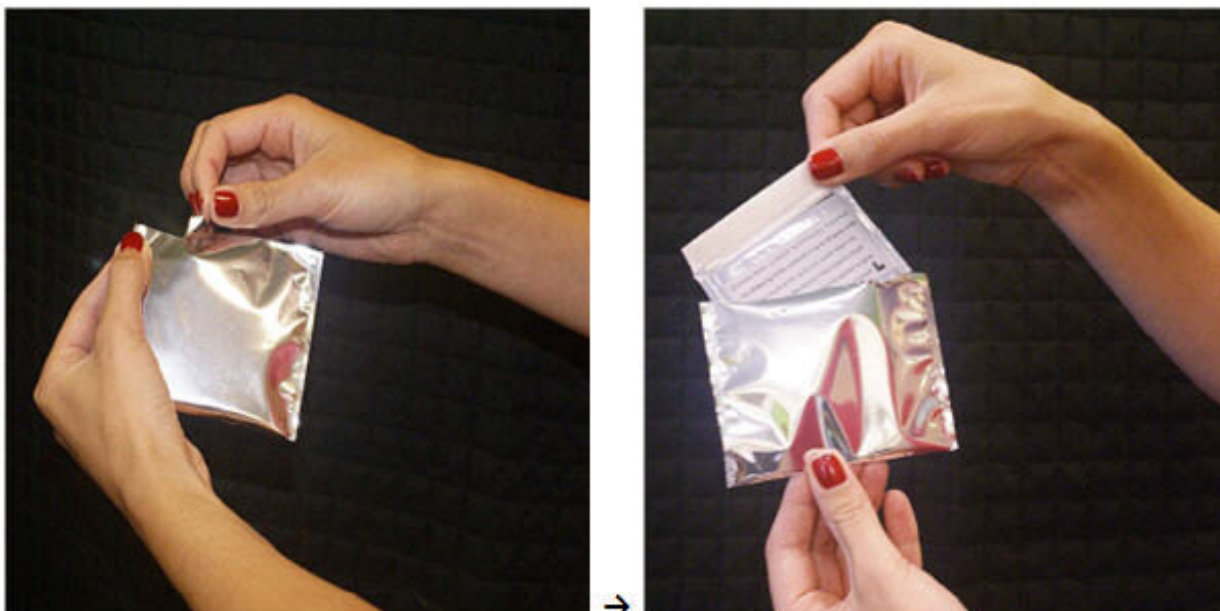


Figure N

- Remove the SUBSYS spray unit from the blister package by cutting the dashed line with a pair of scissors. (See Figure O)



Figure O

- Hold the charcoal-lined disposal pouch with the opening facing up. Put the nozzle of the SUBSYS spray unit upside-down into the opening of the charcoal-lined disposal pouch. (See **Figure P**)



Figure P

- Squeeze your fingers and thumb together to spray SUBSYS into the charcoal-lined disposal pouch.
- Dispose of the empty spray unit in a disposal bag. (See **Figures K and L**)
- **Repeat steps O and P for each unused SUBSYS spray unit. The charcoal-lined disposal pouch may be used for disposing of the contents of up to 10 spray units.**
- Make sure all unused spray units have been sprayed into a charcoal-lined disposal pouch. To seal a used charcoal-lined disposal pouch, remove the backing from the adhesive strip. (See **Figure Q**) Fold the flap down and press to seal the charcoal-lined disposal pouch.



Figure Q

Place the sealed charcoal-lined disposal pouch into a disposal bag. **(See Figure R)**

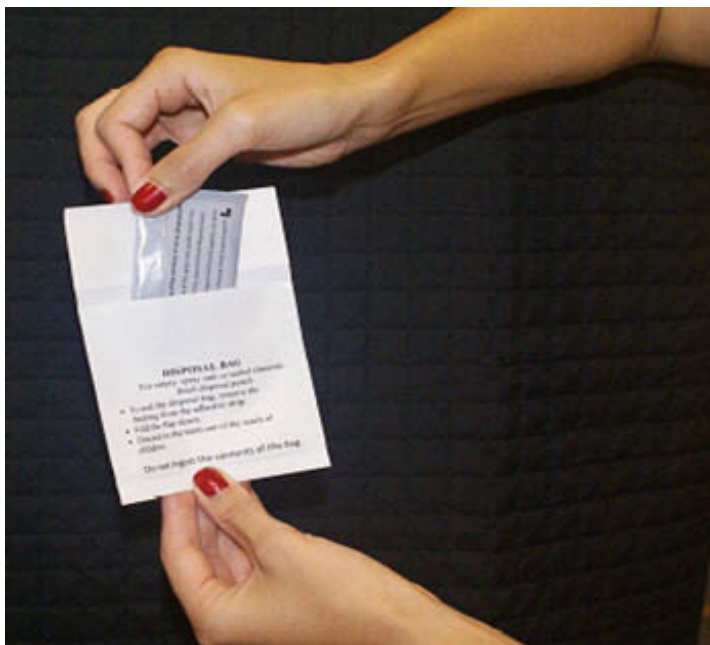


Figure R

- To seal the disposal bag, remove the backing from the adhesive strip. Fold the flap down and press to seal.
- Discard the sealed disposal bag in the trash out of the reach of children. **(See Figure S)**



Figure S

- Do not ingest the contents of the disposal bag.

If you need help with disposal of SUBSYS, call Insys Therapeutics, Inc. at 1-877-978-2797 or call your local Drug Enforcement Agency (DEA) office.

This Medication Guide has been approved by the U.S. Food and Drug Administration.

Manufactured by:

DPT Laboratories, Ltd., Lakewood, NJ 08701

for:

Insys Therapeutics, Inc., Chandler, AZ 85286

Revised December 2014

122414

PRINCIPAL DISPLAY PANEL - 100 mcg Bottle Blister Pack

NDC 20482-001-01

Rx Only

SUBSYS®

fentanyl sublingual spray

CII

100 mcg per spray

For administration under the tongue only.

Dosing must be 4 hours apart.

Use immediately after opening.

See the Medication Guide for instructions for use.

Quantity: The enclosed device unit contains one spray.

WARNING

- **Only for patients taking around-the-clock opioid therapy.**
- **Keep in a safe place away from children.**
- **Can be harmful or fatal to someone for whom it was not prescribed.**

Store at 20-25°C (68-77°F), excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature].

0.1 mL per unit

**INSYS
THERAPEUTICS, INC.**

150-07098

Lot#: 0000000

Exp: MM/YYYY

<p>NDC 20482-001-01 Rx Only</p> <p>SUBSYS® CII fentanyl sublingual spray 100 mcg per spray</p> <p>For administration under the tongue only. Dosing must be 4 hours apart. Use immediately after opening. See the Medication Guide for instructions for use. Quantity: The enclosed device unit contains one spray.</p> <p>WARNING</p> <ul style="list-style-type: none">• Only for patients taking around-the-clock opioid therapy.• Keep in a safe place away from children.• Can be harmful or fatal to someone for whom it was not prescribed. <p>Store at 20-25°C (68-77°F), excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature].</p> <p>0.1 mL per unit insys THERAPEUTICS, INC. 150-07098</p> <p>Lot#: 0000000 Exp: MM/YYYY</p> <p>3 20482 00101 3</p>	<p>NDC 20482-001-01 Rx Only</p> <p>SUBSYS® CII fentanyl sublingual spray 100 mcg per spray</p> <p>For administration under the tongue only. Dosing must be 4 hours apart. Use immediately after opening. See the Medication Guide for instructions for use. Quantity: The enclosed device unit contains one spray.</p> <p>WARNING</p> <ul style="list-style-type: none">• Only for patients taking around-the-clock opioid therapy.• Keep in a safe place away from children.• Can be harmful or fatal to someone for whom it was not prescribed. <p>Store at 20-25°C (68-77°F), excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature].</p> <p>0.1 mL per unit insys THERAPEUTICS, INC. 150-07098</p> <p>Lot#: 0000000 Exp: MM/YYYY</p> <p>3 20482 00101 3</p>
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PRINCIPAL DISPLAY PANEL - 200 mcg Bottle Blister Pack

NDC 20482-002-01

Rx Only

SUBSYS®
fentanyl sublingual spray
CII

200 mcg per spray

For administration under the tongue only.

Dosing must be 4 hours apart.

Use immediately after opening.

See the Medication Guide for instructions for use.

Quantity: The enclosed device unit contains one spray.

WARNING

- **Only for patients taking around-the-clock opioid therapy.**
- **Keep in a safe place away from children.**
- **Can be harmful or fatal to someone for whom it was not prescribed.**

Store at 20-25°C (68-77°F), excursions permitted to 15-30°C (59-86°F)
[see USP Controlled Room Temperature].

0.1 mL per unit

INSYS

THERAPEUTICS, INC.

150-07099

Lot#: 0000000

Exp: MM/YYYY



PRINCIPAL DISPLAY PANEL - 400 mcg Bottle Blister Pack

NDC 20482-004-01

Rx Only

SUBSYS®

fentanyl sublingual spray

C II

400 mcg per spray

For administration under the tongue only.

Dosing must be 4 hours apart.

Use immediately after opening.

See the Medication Guide for instructions for use.

Quantity: The enclosed device unit contains one spray.

WARNING

- **Only for patients taking around-the-clock opioid therapy.**
- **Keep in a safe place away from children.**
- **Can be harmful or fatal to someone for whom it was not prescribed.**

Store at 20-25°C (68-77°F), excursions permitted to 15-30°C (59-86°F)
[see USP Controlled Room Temperature].

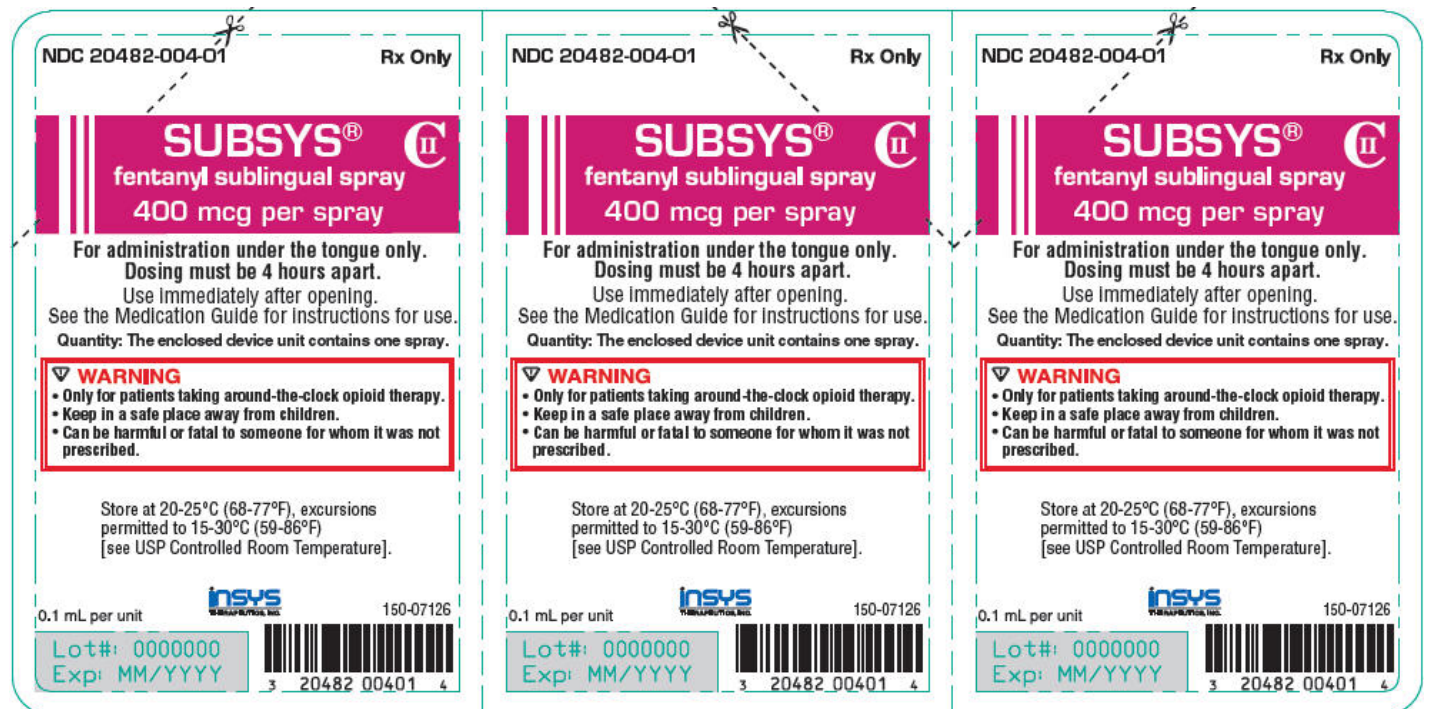
0.1 mL per unit

**INSYS
THERAPEUTICS, INC.**

150-07126

Lot#: 0000000

Exp: MM/YYYY



PRINCIPAL DISPLAY PANEL - 600 mcg Bottle Blister Pack

NDC 20482-006-01

Rx Only

**SUBSYS®
fentanyl sublingual spray
CII**

600 mcg per spray

For administration under the tongue only.

Dosing must be 4 hours apart.

Use immediately after opening.

See the Medication Guide for instructions for use.

Quantity: The enclosed device unit contains one spray.

WARNING

- **Only for patients taking around-the-clock opioid therapy.**
- **Keep in a safe place away from children.**
- **Can be harmful or fatal to someone for whom it was not prescribed.**

Store at 20-25°C (68-77°F), excursions permitted to 15-30°C (59-86°F)
[see USP Controlled Room Temperature].

0.1 mL per unit

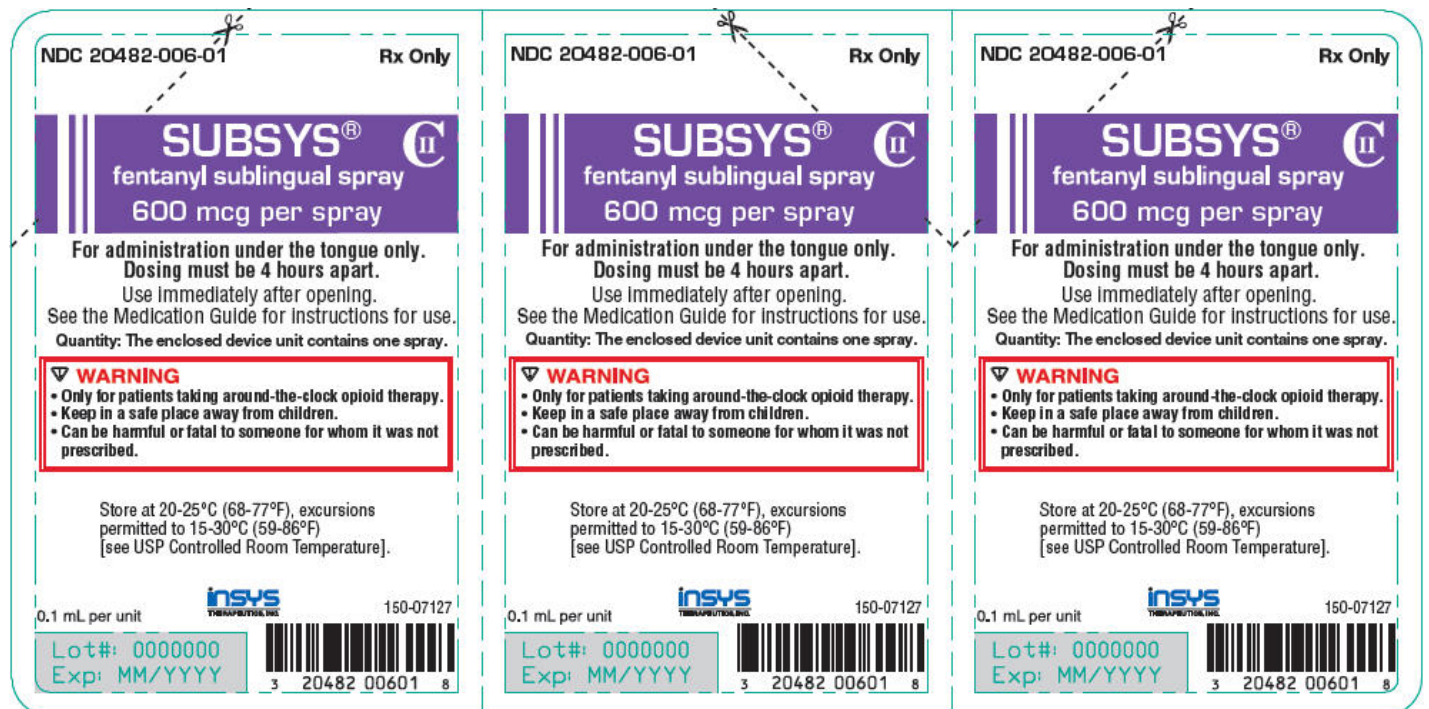
INSYS

THERAPEUTICS, INC.

150-07127

Lot#: 0000000

Exp: MM/YYYY



PRINCIPAL DISPLAY PANEL - 800 mcg Bottle Blister Pack

NDC 20482-008-01

Rx Only

SUBSYS®

fentanyl sublingual spray

CII

800 mcg per spray

For administration under the tongue only.

Dosing must be 4 hours apart.

Use immediately after opening.

See the Medication Guide for instructions for use.

Quantity: The enclosed device unit contains one spray.

WARNING

- Only for patients taking around-the-clock opioid therapy.
- Keep in a safe place away from children.
- Can be harmful or fatal to someone for whom it was not prescribed.

Store at 20-25°C (68-77°F), excursions permitted to 15-30°C (59-86°F)
[see USP Controlled Room Temperature].

0.1 mL per unit

INSYS

THERAPEUTICS, INC.

150-07128

Lot#: 0000000

Exp: MM/YYYY



PRINCIPAL DISPLAY PANEL - 2 x 600 mcg Bottle Blister Pack

NDC 20482-012-01

Rx Only

SUBSYS®

fentanyl sublingual spray

CII

1200 mcg

(supplied as two 600 mcg device units)

For administration under the tongue only.

Dosing must be 4 hours apart.

Use two sprays (one spray from each device) to achieve a total of 1200 mcg.

Use immediately after opening.

See the Medication Guide for instructions for use.

Quantity: The enclosed device units contain one spray each.

WARNING

- **Only for patients taking around-the-clock opioid therapy.**
- **Keep in a safe place away from children.**
- **Can be harmful or fatal to someone for whom it was not prescribed.**

Store at 20-25°C (68-77°F), excursions permitted to
15-30°C (59-86°F) [see USP Controlled Room Temperature].

0.1 mL per unit

150-07150

Lot#: 0000000

Exp: MM/YYYY

INSYS

THERAPEUTICS, INC.

NDC 20482-012-01

Rx Only

SUBSYS[®] **CII**

fentanyl sublingual spray

1200 mcg

(supplied as two 600 mcg device units)

For administration under the tongue only.

Dosing must be 4 hours apart.

Use two sprays (one spray from each device) to achieve a total of 1200 mcg.

Use immediately after opening.

See the Medication Guide for instructions for use.

Quantity: The enclosed device units contain one spray each.

⚠ WARNING

- Only for patients taking around-the-clock opioid therapy.
- Keep in a safe place away from children.
- Can be harmful or fatal to someone for whom it was not prescribed.

Store at 20-25°C (68-77°F), excursions permitted to
15-30°C (59-86°F) [see USP Controlled Room Temperature].

0.1 mL per unit

Lot#: 0000000
Exp: MM/YYYY

insys
THERAPEUTICS, INC.



PRINCIPAL DISPLAY PANEL - 2 x 800 mcg Bottle Blister Pack

NDC 20482-016-01

Rx Only

SUBSYS[®]

fentanyl sublingual spray

CII

1600 mcg

(supplied as two 800 mcg device units)

For administration under the tongue only.

Dosing must be 4 hours apart.

Use two sprays (one spray from each device) to achieve a total of 1600 mcg.

Use immediately after opening.

See the Medication Guide for instructions for use.

Quantity: The enclosed device units contain one spray each.

WARNING

- Only for patients taking around-the-clock opioid therapy.
- Keep in a safe place away from children.
- Can be harmful or fatal to someone for whom it was not prescribed.

Store at 20-25°C (68-77°F), excursions permitted to

15-30°C (59-86°F) [see USP Controlled Room Temperature].

0.1 mL per unit

150-07129

Lot#: 0000000

Exp: MM/YYYY

INSYS

THERAPEUTICS, INC.

NDC 20482-016-01 Rx Only

SUBSYS[®] **CII**
fentanyl sublingual spray
1600 mcg
(supplied as two 800 mcg device units)

For administration under the tongue only.
Dosing must be 4 hours apart.
Use two sprays (one spray from each device) to achieve a total of 1600 mcg.
Use immediately after opening.
See the Medication Guide for instructions for use.
Quantity: The enclosed device units contain one spray each.


⚠ WARNING


- Only for patients taking around-the-clock opioid therapy.
- Keep in a safe place away from children.
- Can be harmful or fatal to someone for whom it was not prescribed.

Store at 20-25°C (68-77°F), excursions permitted to
15-30°C (59-86°F) [see USP Controlled Room Temperature].

0.1 mL per unit

Lot#: 0000000
Exp: MM/YYYY




150-07129
3 20482 01601 7

SUBSYS

fentanyl spray

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:20482-001
Route of Administration	SUBLINGUAL	DEA Schedule	CII

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
FENTANYL (UNII: UF599785JZ) (FENTANYL - UNII:UF599785JZ)	FENTANYL	0.1 mg

Inactive Ingredients	
Ingredient Name	Strength
alcohol (UNII: 3K9958V90M)	
water (UNII: 059QF0KO0R)	
propylene glycol (UNII: 6DC9Q167V3)	
xylitol (UNII: VCQ006KQ1E)	
levomenthol (UNII: BZ1R15MTK7)	

Packaging				
#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:20482-001-30	30 in 1 CARTON		
1		1 in 1 BLISTER PACK		
1		1 in 1 BOTTLE, SPRAY; Type 2: Prefilled Drug Delivery Device/System (syringe, patch, etc.)		
2	NDC:20482-001-10	10 in 1 CARTON		
2		1 in 1 BLISTER PACK		
2		1 in 1 BOTTLE, SPRAY; Type 2: Prefilled Drug Delivery Device/System (syringe, patch, etc.)		

Marketing Information			
Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA202788	03/13/2012	

SUBSYS			
fentanyl spray			
Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:20482-002
Route of Administration	SUBLINGUAL	DEA Schedule	CII
Active Ingredient/Active Moiety			
Ingredient Name		Basis of Strength	Strength
FENTANYL (UNII: UF599785JZ) (FENTANYL - UNII:UF599785JZ)		FENTANYL	0.2 mg
Inactive Ingredients			
Ingredient Name			Strength
alcohol (UNII: 3K9958V90M)			
water (UNII: 059QF0KO0R)			

propylene glycol (UNII: 6DC9Q167V3)	
xylitol (UNII: VCQ006KQ1E)	
levomenthol (UNII: BZ1R15MTK7)	

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:20482-002-30	30 in 1 CARTON		
1		1 in 1 BLISTER PACK		
1		1 in 1 BOTTLE, SPRAY; Type 2: Prefilled Drug Delivery Device/System (syringe, patch, etc.)		
2	NDC:20482-002-10	10 in 1 CARTON		
2		1 in 1 BLISTER PACK		
2		1 in 1 BOTTLE, SPRAY; Type 2: Prefilled Drug Delivery Device/System (syringe, patch, etc.)		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA202788	03/13/2012	

SUBSYS

fentanyl spray

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:20482-004
Route of Administration	SUBLINGUAL	DEA Schedule	CII

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
FENTANYL (UNII: UF599785JZ) (FENTANYL - UNII:UF599785JZ)	FENTANYL	0.4 mg

Inactive Ingredients

Ingredient Name	Strength
alcohol (UNII: 3K9958V90M)	
water (UNII: 059QF0KO0R)	
propylene glycol (UNII: 6DC9Q167V3)	
xylitol (UNII: VCQ006KQ1E)	
levomenthol (UNII: BZ1R15MTK7)	

Packaging				
#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:20482-004-30	30 in 1 CARTON		
1		1 in 1 BLISTER PACK		
1		1 in 1 BOTTLE, SPRAY; Type 2: Prefilled Drug Delivery Device/System (syringe, patch, etc.)		
2	NDC:20482-004-10	10 in 1 CARTON		
2		1 in 1 BLISTER PACK		
2		1 in 1 BOTTLE, SPRAY; Type 2: Prefilled Drug Delivery Device/System (syringe, patch, etc.)		
Marketing Information				
Marketing Category		Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA		NDA202788	03/13/2012	

SUBSYS					
fentanyl spray					
Product Information					
Product Type		HUMAN PRESCRIPTION DRUG	Item Code (Source)		NDC:20482-006
Route of Administration		SUBLINGUAL	DEA Schedule		CII
Active Ingredient/Active Moiety					
Ingredient Name			Basis of Strength		Strength
FENTANYL (UNII: UF599785JZ) (FENTANYL - UNII:UF599785JZ)			FENTANYL		0.6 mg
Inactive Ingredients					
Ingredient Name				Strength	
alcohol (UNII: 3K9958V90M)					
water (UNII: 059QF0KO0R)					
propylene glycol (UNII: 6DC9Q167V3)					
xylitol (UNII: VCQ006KQ1E)					
levomenthol (UNII: BZ1R15MTK7)					
Packaging					
#	Item Code	Package Description		Marketing Start Date	Marketing End Date
1	NDC:20482-006-30	30 in 1 CARTON			
1		1 in 1 BLISTER PACK			

1		1 in 1 BOTTLE, SPRAY; Type 2: Prefilled Drug Delivery Device/System (syringe, patch, etc.)		
2	NDC:20482-006-10	10 in 1 CARTON		
2		1 in 1 BLISTER PACK		
2		1 in 1 BOTTLE, SPRAY; Type 2: Prefilled Drug Delivery Device/System (syringe, patch, etc.)		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA202788	03/13/2012	

SUBSYS

fentanyl spray

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:20482-008
Route of Administration	SUBLINGUAL	DEA Schedule	CII

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
FENTANYL (UNII: UF599785JZ) (FENTANYL - UNII:UF599785JZ)	FENTANYL	0.8 mg

Inactive Ingredients

Ingredient Name	Strength
alcohol (UNII: 3K9958V90M)	
water (UNII: 059QF0KO0R)	
propylene glycol (UNII: 6DC9Q167V3)	
xylitol (UNII: VCQ006KQ1E)	
levomenthol (UNII: BZ1R15MTK7)	

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:20482-008-30	30 in 1 CARTON		
1		1 in 1 BLISTER PACK		
1		1 in 1 BOTTLE, SPRAY; Type 2: Prefilled Drug Delivery Device/System (syringe, patch, etc.)		
2	NDC:20482-008-10	10 in 1 CARTON		
2		1 in 1 BLISTER PACK		
2		1 in 1 BOTTLE, SPRAY; Type 2: Prefilled Drug Delivery Device/System (syringe, patch, etc.)		

Marketing Information			
Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA202788	03/13/2012	

SUBSYS
fentanyl spray

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:20482-012
Route of Administration	SUBLINGUAL	DEA Schedule	CII

Active Ingredient/Active Moiety		
Ingredient Name	Basis of Strength	Strength
FENTANYL (UNII: UF599785JZ) (FENTANYL - UNII:UF599785JZ)	FENTANYL	0.6 mg

Inactive Ingredients	
Ingredient Name	Strength
alcohol (UNII: 3K9958V90M)	
water (UNII: 059QF0KO0R)	
propylene glycol (UNII: 6DC9Q167V3)	
xylitol (UNII: VCQ006KQ1E)	
levomenthol (UNII: BZ1R15MTK7)	

Packaging				
#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:20482-012-15	15 in 1 CARTON		
1		2 in 1 BLISTER PACK		
1		1 in 1 BOTTLE, SPRAY; Type 2: Prefilled Drug Delivery Device/System (syringe, patch, etc.)		

Marketing Information			
Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA202788	08/30/2012	

SUBSYS
fentanyl spray

Product Information				
Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:20482-016	
Route of Administration	SUBLINGUAL	DEA Schedule	CII	
Active Ingredient/Active Moiety				
Ingredient Name		Basis of Strength	Strength	
FENTANYL (UNII: UF599785JZ) (FENTANYL - UNII:UF599785JZ)		FENTANYL	0.8 mg	
Inactive Ingredients				
Ingredient Name			Strength	
alcohol (UNII: 3K9958V90M)				
water (UNII: 059QF0KO0R)				
propylene glycol (UNII: 6DC9Q167V3)				
xylitol (UNII: VCQ006KQ1E)				
levomenthol (UNII: BZ1R15MTK7)				
Packaging				
#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:20482-016-15	15 in 1 CARTON		
1		2 in 1 BLISTER PACK		
1		1 in 1 BOTTLE, SPRAY; Type 2: Prefilled Drug Delivery Device/System (syringe, patch, etc.)		
Marketing Information				
Marketing Category		Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA		NDA202788	08/30/2012	

Labeler - Insys Therapeutics, Inc. (803052443)

Revised: 1/2015

Insys Therapeutics, Inc.